Progress and current challenges in the management of invasive fungal infections in hematologic malignancy patients and allogeneic hematopoietic cell transplant recipients

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"Progress and current challenges in the management of invasive fungal infections in hematologic malignancy patients and allogeneic hematopoietic cell transplant recipients"

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SUMMARY

Invasive aspergillosis (IA) is a common complication in allogeneic hematopoietic cell transplant (HCT) recipients, associated with high mortality and morbidity rates. Significant improvement in overall survival in patients with IA has been demonstrated in the post-voriconazole era. However, voriconazole may be discontinued in up to 40-45% of allogeneic HCT recipients, who receive this agent as primary antifungal prophylaxis. This is due to a number of limitations, associated with voriconazole, including hepatotoxicity, neurotoxicity, co-administration with cyclodextrin for the intravenously administered voriconazole formulation, and important drug-drug interactions. Additional options exist, with isavuconazole and posaconazole representing effective and safe treatments for IA. Isavuconazole was found non-inferior and better tolerated than voriconazole, in a prospective, randomized, non-inferiority international clinical trial. Similarly, posaconazole was recently shown to be non-inferior to voriconazole for the treatment of IA, also with a more favorable side effect profile. However, posaconazole use may be hindered by the large variability of blood concentrations observed and the important drug-drug interactions, as a result of its complex metabolism. Considering the above, it is evident that none of the available treatments for IA has an optimal toxicity and drug-drug interaction profile. Moreover, existing data suggest that all-cause 6- and 12-week mortality in patients with IA have remained in the range of 20% and 35%, respectively, since the early 2000s. Hence, despite the progress attained in the fields of infectious diseases and hematology / HCT, clinical outcomes in patients with IA have stagnated during the last two decades due to a variety of reasons. Whether the existing gap of 20-30% in all-cause mortality may be further decreased remains to be discussed. No new antifungal agent classes have been introduced in clinical practices since echinocandins in the early 2000s. However, for the first time after many decades, new classes of antifungals are under consideration and clinical investigation. Some of those new agents / classes appear to have excellent activity against most *Aspergillus* species and favorable pharmacokinetic and toxicity profiles. In addition to the available treatment options, genetic factors may eventually prove to be important players in the fight against IA. A number of genetic polymorphisms have been associated with susceptibility to different infections, including IA. The effect of genetic factors as such on clinical outcomes has not been, as yet, further studied. However, the realization that underlying genetic factors may impact clinical outcomes may open new opportunities in the field of invasive fungal infections. To conclude, significant progress has been attained in the management of IA in allogeneic HCT recipients, with the new generation azoles having dominated the field during the last two decades, offering viable, effective and safe treatment options. Having achieved a plateau in overall survival since the early 2000s, it is time to explore additional options, including new antifungal treatments and personalized medicine approaches, in

order to further improve clinical outcomes and survival in allogeneic HCT recipients with a severe infection due to *Aspergillus* spp. and other molds.

INTRODUCTION

Invasive fungal infections in high-risk hematology patients

Patients with hematologic malignancies and allogeneic hematopoietic cell transplant (HCT) recipients are at risk for opportunistic infections, including invasive fungal infections (IFI), as a result of their underlying pathologies and administered treatments (1-3). Prolonged and profound neutropenia due to an underlying leukemia or intensive chemotherapy administration is a known risk factor for IFI. In addition, administration of T-cell depleting treatments, including high-dose steroids for the management of acute or chronic graft-versus-host disease (GvHD), thymoglobulin, or alemtuzumab, increase the risk for invasive mold infections (IMI), including infections due to *Aspergillus* spp., *Mucorales*, and other filamentous fungi (1, 4). Furthermore, chemotherapy-related mucositis is a well-known risk factor for translocation of gastro-intestinal flora, including *Candida* spp. (3).

In fact, invasive candidiasis was the first IFI to be identified as a significant infectious disease complication in high-risk hematology patients, including autologous and allogeneic HCT recipients already in the 1980s (4-7). As a result, antifungal prophylaxis clinical trials, reported in the early 1990s, supported and established the administration of fluconazole as routine primary antifungal prophylaxis during the first 75-100 days after an HCT (8, 9) . More than twenty years later, fluconazole remains the backbone of antifungal prophylaxis in the setting, as illustrated in international guidelines (3, 10, 11). However, soon after fluconazole was introduced as routine antifungal prophylaxis and the incidence of invasive candidiasis plummeted, two additional problems emerged.

(1) The epidemiology of *Candida* infections started changing, with non-*albicans Candida* spp. becoming the predominant cause of candida infections in high-risk hematology patients (4, 6, 7, 12-15).

(2) In addition, the incidence of IMI, particularly those caused by *Aspergillus* spp., significantly increased through the years, with incidence rates reported in the range of 10 to 15% in the late 1990s (1, 2, 16-23).

Incidence of invasive aspergillosis in high-risk hematology patients

A diagnosis of an IMI in the 1990s was associated with a mortality as high as 90% at 1-year post-HCT and significant associated morbidity (24, 25). The higher incidence of IMI reported in the 1990s and 2000s may be, in part, associated with a number of different reasons, including, but not limited to:

(1) The ongoing changes in chemotherapy regimens in patients with acute myelogenous leukemia (AML) and HCT-associated practices (e.g. conditioning regimens, HCT source and donor selection, graft manipulation and others).
(2) Accepting higher risk and older patients for an allogeneic HCT.
(3) Improved patient care, allowing high-risk patients to live longer and therefore remain at risk for an IMI for longer periods of time.
(4) An additional reason that could have contributed to the higher rates of IMI documented in high-risk patients has been the fact that our ability to establish the diagnosis of an IMI has significantly improved with time, due to our better understanding of the pathophysiology, timing and associated risk factors for those infections, but also the significant progress attained in the field of diagnostics.

The above have allowed us to be more vigilant and adjust our diagnostic and therapeutic interventions in a timely fashion on a case-by-case basis.

Clinical outcomes of invasive aspergillosis

Since the 1990s and mortality rates in the range of 70-90%, we have managed to decrease the mortality of this infection in the range of 15-30% in today's world (25-27). This has been made possible due to a large variety of reasons, which can be summarized under the following three major pillars:

(1) diagnostics,
(2) treatment, and
(3) prophylaxis.

In the following pages of this Introduction, a brief review and discussion of these major three pillars, which have shaped the clinical practice of hematology patients and the management of IA will be presented.

Diagnosis of invasive aspergillosis

The progress attained in the field of diagnosis of IA through the years has been spectacular. This has included three major axes:

(1) better understanding of the pathophysiology and identification of risk factors for IA,
(2) optimized use of imaging tests, and
(3) development of fungal biomarkers and molecular tests.

Pathophysiology and risk factors of invasive aspergillosis

It is important to emphasize that through the years we were able to better understand the pathophysiology of this infection and identify significant predictors. For instance, early on we were able to define time periods at risk for IA, including pre-engraftment due to prolonged and profound neutropenia and post-engraftment due to moderate to severe GvHD requiring treatment with high-dose corticosteroids and other immunosuppressive treatemnts. Administration of T-cell depleted grafts or T-cell depleting agents, concomitant infection with cytomegalovirus (CMV) or respiratory viruses have been well-established risk factors for IA after an allogeneic HCT (1, 2, 16, 25, 26, 28, 29). This knowledge has enabled clinicians to appreciate which patients are more at risk to develop IA and at which point and hence providing them with the ability to develop an early clinical suspicion for this infection and initiate a more aggressive and detailed diagnostic work-up and promptly initiate an empirical or pre-emptive antifungal treatment. Although today this seems almost intuitive, it took decades of dedicated research efforts to detect and identify strong and valid associations to guide clinical practice. Similarly, the identification of “at risk” periods, such as pre- and post-engraftment helped better describe the timing of such infections, again allowing clinicians to better tailor their diagnostic and therapeutic interventions. More recently, genetic polymorphisms have been proposed as additional risk factors, predisposing patients to higher rates of IMI, including IA (30-37). Although data on genetic risk factors have been increasingly reported since the early 2000s, as yet, they have not been incorporated in clinical practice.

Imaging and invasive aspergillosis

The introduction of computed tomography (CT) of sinuses and chest and the identification of specific CT findings, such as the “halo”, “reverse halo” and “crescent” signs, has significantly improved our ability to identify patients with lesions suspicious for an IMI and initiate a prompt and appropriate diagnostic work-up and introduction of preemptive treatment (38, 39). Notably, the identification of a “halo sign” has been associated with improved clinical outcomes, most likely as a result of prompt initiation of appropriate preemptive antifungal treatment (39, 40). The importance of CT in the diagnosis of IA is further illustrated by the inclusion of a chest and/or sinus CT scan in the context of unexplained persistent neutropenic fever in consensus guidelines (11, 41, 42). Suspicious CT findings may prompt further diagnostic work-up, such as a bronchoscopy or sinus examination and debridement, but also initiation of appropriate antifungal treatment.

In addition to the classic “halo” and “crescent” signs, we have been able to appreciate that an IMI may actually present with even less typical radiographic images, including consolidations, pleural

effusions, and also ground-glass opacities, particularly in patients with GvHD and other patient categories, such as solid organ transplant recipients (43). This is quite pertinent, as the vast majority of patients will not have the typical appearance of a chest CT with a nodular lesion and a "halo sign" but may present with a large variety of radiographic findings. Although those atypical radiographic presentations are not, as yet, part of the consensus definitions of IFIs, they have significantly increased our ability for early detection and treatment of IMI, including IA.

Fungal biomarkers and molecular tests

Establishing the diagnosis of IFI due to filamentous fungi has suffered due to the relatively problematic performance of traditional diagnostics, such as the fungal stain and culture (44-47). Since the early 2000s, the galactomannan enzyme immunoassay (GM EIA) has become one of the most important diagnostic biomarkers in clinical practice (48-57). Despite the fact that a lot of controversy existed in the beginning, particularly in terms of the optimal optical density index (ODI) cutoff and the frequency of screening, the GM EIA is now routinely used as a screening and diagnostic test in most transplant and hematology centers around the globe. Its performance may depend on a number of variables, including the presence or not of neutropenia and GvHD, the age of the patient, the co-administration of antifungal prophylaxis or certain antibacterial agents, and others (49, 51, 54, 58-63). It may not necessarily be specific to *Aspergillus* species, as other *Ascomycetes* may produce a positive GM EIA result (49). Nevertheless, this test has become one of the most frequently used tests in clinical practice of high-risk hematology patients and its use has revolutionized the care of our patients and allowed us to establish a potential diagnosis, without the absolute need to perform an invasive diagnostic procedure. In addition, GM EIA may provide us with a diagnosis at a much earlier stage of the infection, thereby allowing the prompt introduction of appropriate antifungal treatment (54, 64).

Routine screening of high-risk patients once or twice weekly with GM EIA has been shown to increase the diagnostic yield of IFI in the setting and allow prompt treatment initiation (63-66). Considering its water-soluble nature, the GM nay be measured in non-blood samples as well, including the bronchoalveolar lavage (BAL), pleural fluid, or cerebrospinal fluid (CSF) (64). In addition to GM EIA, another fungal biomarker, the beta-D-glucan (β-DG) has also significantly improved our ability to establish the diagnosis of an IFI (67-69). In contrast to GM, the β-DG is less specific to IA, as most fungal pathogens may produce a positive β-DG result (64, 70, 71).

Once a clinical suspicion for a possible IFI is documented on a sinus or chest CT, a diagnostic procedure, such as a bronchoscopy or sinus investigation, is then required. Although an interventional diagnostic procedure, data from a single center retrospective cohort study have clearly shown that a bronchoscopy is a well-tolerated and safe procedure even in high-risk patients with profound thrombocytopenia (72). A more invasive procedure, such as a transbronchial or even a lung tissue biopsy is occasionally required to establish a definitive diagnosis (and at times as a therapeutic intervention as well). Once a diagnostic sample is obtained, an long array of diagnostic microbiology tests can be added, including, fungal stains and cultures, but also a GM EIA and –more recently- a molecular test, such as a polymerase chain reaction (PCR), for *Aspergillus, Mucorales* or a panfungal PCR assay may be performed. While the performance and reproducibility of results from different molecular assays used at different laboratories remain to be validated, current data suggest that the addition of a fungal PCR on appropriate specimens may significantly help obtain a microbiological diagnosis in a number of cases, where a negative culture would prevent a microbiologically confirmed diagnosis of an IMI (73).

Using all the above-mentioned diagnostic tools, currently we are able to accurately and promptly make the diagnosis of IA or another IMI in most high-risk hematology patients with those infections. The earlier the diagnosis is made, the faster appropriate treatment is initiated, and the better are the outcomes. However, if treatment options were limited to amphotericin-B products, which suffer from associated toxicities, namely nephrotoxicity and infusion related reactions, treatment initiation upon clinical suspicion would not be as prompt, due to the limitations associated with those very side effects (74, 75). Hence, a low threshold for empirical or preemptive antifungal treatment initiation requires a high clinical suspicion, positive surrogate diagnostic tests, but also safe and well-tolerated treatments, treatments that would do “more good than harm”.

Treatment of invasive aspergillosis

Voriconazole efficacy

Voriconazole is a broad-spectrum azole with activity against most *Aspergillus* spp. and other filamentous fungi, but not against the *Mucorales*, and has been validated as first-line treatment for the treatment of IA, based on significantly improved survival when compared to conventional amphotericin-B (75). In the pivotal registration clinical trial, 12-week survival was significantly higher in the voriconazole versus the amphotericin-B arm. The favorable outcomes associated with voriconazole are not only due to the efficacy of this agent, but also a result of its favorable side-effect profile vis-à-vis amphotericin-B deoxycholate. The high rates of nephrotoxicity associated with the

use of amphotericin-B products, including the lipid-formulations of this agent, have significantly hindered the use of those agents for the treatment of IFI, including IA.

Since then, additional studies have demonstrated the beneficial effect of treatment of IA with voriconazole when compared to amphotericin-B products (76). In contrast to amphotericin-B, voriconazole is not an inherently nephrotoxic agent, allowing the prompt introduction of treatment with this agent, the side effects of which, were considered -until recently- less important to those of amphotericin-B products. In fact, 12-week overall survival after a diagnosis of IA in high-risk allogeneic HCT recipients significantly increased in the range of 65-70% during the voriconazole era (28, 75, 77, 78). As this may be, in part, the result of a combination of variables, the role of voriconazole in the successful management of this infection is undeniable. Based on the above data, voriconazole has been considered as standard of care for the treatment of IA in international guidelines for the treatment of IA (79, 80)

Voriconazole toxicities

Despite its well-established efficacy, a large number of issues associated with voriconazole administration have been identified in clinical practice through the years (81-87). Voriconazole has non-linear pharmacokinetics, therefore voriconazole blood concentrations and dose adjustments are not easily predictable (88-94). It is metabolized predominately through the CYP2C19 but also through the CYP2C9 and CYP3A4 enzymes, while it is a strong inhibitor of CYP3A4, resulting in multiple and important drug-drug interactions with other agents (91). A black box warning for voriconazole in patients treated with sirolimus has been announced (95). In addition, genetic polymorphisms, well described for CYP2C19, may significantly affect its metabolism and therefore attained blood concentrations (96-99).

In addition to the above-mentioned pharmacological properties, one of its most frequently observed side effects includes a potential neurotoxic effect, which appears to be dose-related with blood concentrations >5.5mg/mL (100). Neurotoxicity may present as visual or auditory hallucinations, but also with visual changes (84, 85). In addition, voriconazole, as all other azoles, may cause liver function abnormalities in up to one fourth of patients treated (75, 77, 78, 87, 101). In addition, a number of other, less frequent adverse events, have been reported to be associated with administration of voriconazole, such as photosensitivity skin reactions occasionally leading to skin cancer, cheilitis, QT prolongation, and periostitis (83, 96).

Due to the fact that voriconazole is not a water-soluble molecule, intravenously (IV) administered voriconazole requires the co-administration with a vehicle molecule, the sulphobutylether-β-cyclodextrin (SBECD). Cyclodextrin is thought to accumulate in renal tubules and has been associated with renal toxicity in animal models (102). Although this effect has not –as yet- been demonstrated in humans, based on current recommendations by the Food and Drug Administration (FDA), IV voriconazole should be avoided in patients whose glomerular filtration rate (GFR) is <50 mL/min/m^2 (103).

The potential toxicities of this agent along with the significant drug-drug interactions have made measurement of voriconazole blood concentrations the standard of care. Prospective clinical data have suggested that therapeutic drug monitoring (TDM) of voriconazole may significantly decrease voriconazole-associated toxicities, namely neurotoxicity, but also have an effect on clinical efficacy (92). Current guidelines recommend routine TDM in patients treated with voriconazole (79, 80).

The above suggest that although voriconazole has significantly contributed to improving clinical outcomes, important hurdles may limit our ability to use it in a number of settings. For instance, as already mentioned, administration of IV voriconazole may not be allowed in patients with already impaired renal function (103). However, high-risk hematology patients with IA may already have an impaired renal function, as a result of their already compromised status and other treatments they receive. Liver function impairment is a frequent problem in patients after an allogeneic HCT, occasionally leading to discontinuation of other potentially hepatotoxic agents, including voriconazole (82, 104). The potential drug-drug interactions between this agent and other commonly administered agents, including immunosuppressive agents, pose a number of additional challenges in the management of HCT recipients. Finally, voriconazole may not be well tolerated by a number of patients who develop significant neurotoxicities, such as visual hallucinations, visual discoloration, or confusion. Hence, clinicians frequently face the problem of treating patients with IA, without being able to use voriconazole due to one –or more- of the above mentioned issues.

Isavuconazole efficacy & toxicities

Therefore, an important clinical need became evident soon after voriconazole became the standard treatment for IA: a need for an agent as effective but safer and better tolerated than voriconazole. Isavuconazole is a broad-spectrum azole with activity against *Aspergillus* spp. and other filamentous fungi, including certain *Mucorales* spp. (77, 105, 106). Isavuconazole has an excellent bioavailability and thanks to its water-soluble prodrug isavuconazonium, there is no need for combining this agent

with the potentially nephrotoxic SBECD (106). In contrast to voriconazole, isavuconazole has predictable linear pharmacokinetics and predictable therapeutic blood concentrations can be attained (106). Hence, isavuconazole TDM is not considered necessary, based on preliminary data, but also data coming from real-life experiences showing consistent trough levels of isavuconazole at >1 mg/mL (77, 107-110). Another potential benefit of this agent is its effect on the QTc interval, with patients showing a shortening of their QTc interval when treated with isavuconazole (111). This is quite pertinent as allogeneic HCT recipients and patients with leukemias receive multiple different agents, which could potentially have a prolonging effect on their QTc, including, but not limited to, macrolides and fluoroquinolones. As a result, administering an antifungal treatment, most of the times destined to be continued for prolonged periods of time, without having to regularly monitor someone's heart rate and QTc interval may become useful and facilitate patient care, particularly in the outpatient setting.

A prospective, randomized, non-inferiority clinical trial compared isavuconazole to voriconazole for the treatment of IA in patients with hematologic malignancies and allogeneic HCT recipients (77). This clinical trial demonstrated that isavuconazole was non-inferior to voriconazole, but also better tolerated, with significantly lower rates of hepatotoxicity, neurological and eye-related adverse events and skin reactions. Since then, isavuconazole has been included as first-line treatment for IA in the European Guidelines for the management of IA (79). Multiple real-life cohort studies have demonstrated the efficacy and safety profile of isavuconazole (112-117). When compared to voriconazole, patients on isavuconazole may be at lower risk to develop liver function abnormalities and therefore treatment discontinuation (113). Being able to continue and complete a treatment course for the treatment of a serious and life-threatening infection as IA is of major importance, and it appears to be the case with isavuconazole more so than voriconazole. In addition, other, less frequently encountered side effects associated with voriconazole, such as skin reactions, visual and auditory hallucinations have not- to our knowledge and until today- been linked to isavuconazole.

Posaconazole efficacy & toxicities

Posaconazole is a broad-spectrum azole with activity against *Aspergillus* spp. and other filamentous fungi, including *Mucorales* spp. (118, 119). Similar to voriconazole, IV posaconazole requires co-administration with SBECD (118, 119). Its oral formulation as a suspension suffered from poor absorption and required co-administration with high-fat food, occasionally not well-tolerated by high-risk cancer patients (119-123). However, it is currently available as a delayed release tablet (DRT), which is better absorbed and well-tolerated (124). Posaconazole has been approved as

antifungal prophylaxis in high-risk patients and as salvage treatment for patients with IMI (125-127). Until recently, no data were available for the efficacy and safety of posaconazole as primary treatment for IA. Similar to voriconazole, it may be associated with liver function abnormalities and QTc prolongation (118). Furthermore, it has been associated with hypokalemia and pseudo-hyperaldosteronism (128-131).

In a recently published prospective, randomized, double-blind, double-dummy non-inferiority clinical trial posaconazole was compared to voriconazole as primary treatment of IA (78). This clinical trial demonstrated that posaconazole was non-inferior to voriconazole, with all-cause mortality by 42 days post treatment initiation at 15% and 21% in the posaconazole and voriconazole groups, respectively. Posaconazole was also better tolerated, with significantly lower rates of hepatotoxicity, neurological and eye-related adverse events and skin reactions. As the results of this study were made available prior to the publication of the most recent IA treatment guidelines, posaconazole is not included in the preferred treatments for this infection for the time being (79, 80).

Antifungal prophylaxis

Fluconazole

The 1990s were marked by the introduction of fluconazole as effective and safe primary antifungal prophylaxis in allogeneic and autologous HCT recipients (8, 9, 132). This was based on the results of two prospective randomized placebo-controlled clinical trials that clearly demonstrated a significant benefit of fluconazole prophylaxis in terms of decreasing the incidence of invasive candidiasis and –in one study- overall mortality as well (8, 9). This approach had as a result a significant drop in the rates of invasive candidiasis due to gastrointestinal translocation of *Candida* spp. in patients with chemotherapy-associated mucositis (12). Since then, primary antifungal prophylaxis with fluconazole is recommended based on international consensus guidelines for the first 75 to 100 days after an allogeneic HCT, but also until neutropenia resolution in autologous HCT recipients and patients with acute myeloid leukemia treated with intensive chemotherapy (3, 10, 11, 41, 42, 133).

Although the introduction of this approach has significantly improved clinical outcomes and overall survival rates, there were two major issues that came out as a result: (i) a shift in the epidemiology of *Candida* spp., with non-*albicans Candida* spp. becoming the predominant culprit in patients with invasive candidiasis and (ii) more non-*Candida* IFI, mainly IMI due to *Aspergillus* spp. and more rarely due to *Mucorales*, *Fusarium* spp. or *Scedosporium* spp. emerging as significant pathogens (1, 2, 12, 25, 26, 28). The emergence of IMI as a significant problem in allogeneic HCT recipients has been

nicely described in the literature with rates as high as 11-15% recorded in different series and discussed in the first part of this Introduction (1, 2, 12, 25, 26, 28).

Posaconazole

The medical community responded to this unmet need with the introduction of a new broad-spectrum azole, posaconazole (118, 119, 122, 134). As previously discussed, posaconazole has activity against most *Candida*, but also against molds, including *Aspergillus* and *Mucorales* spp. and therefore was a desirable agent in the setting of high-risk patients for an IMI (118, 119). Posaconazole has been validated as primary antifungal prophylaxis in patients with acute myelogenous leukemia with anticipated neutropenia for ≥14 days and in allogeneic HCT recipients with GvHD requiring treatment with high-dose steroids (125, 127). Two clinical trials comparing posaconazole to fluconazole in these two different patient populations demonstrated a significant drop on the incidence of IMI in those patients treated with posaconazole when compared to fluconazole, while a survival benefit was also demonstrated in one of the two studies (125, 127). As a result, posaconazole has become the standard of care as primary antifungal prophylaxis in these patient populations since then (3, 11, 41, 42, 133).

Considerations on antifungal prophylaxis

Although the introduction of posaconazole has significantly impacted the incidence of IA in high-risk patient populations, breakthrough IMI have been increasingly observed (112, 135-142). Posaconazole-breakthrough IMI are frequently due to molds that are harder to treat than *Aspergillus fumigatus* infections, such *A. ustus*, *Mucorales*, *Scedosporium* spp., and other less frequently encountered molds. In addition, a number of other issues have been made evident since the routine use of posaconazole as primary antifungal prophylaxis, which further complicate the utilization of this agent in the setting. For instance, posaconazole being a moderate-to-strong CYP3A4 inhibitor has significant interactions with a number of agents, commonly used in the care of hematology patients. More recently, posaconazole has been identified to have significant interactions with new chemotherapy molecules increasingly used in the care of leukemia patients, such as midostaurin and venetoclax (143, 144). In addition, like most other azoles, posaconazole has been associated with hepatotoxicity, a common problem in allogeneic HCT recipients (118, 119, 134).

All that, when concerns that the number of patients needed to treat with posaconazole to prevent one IFI may be too high have been expressed (145). Hence, identifying patients who would benefit the most from the administration of primary prophylaxis with a broad-spectrum antifungal agent,

such as posaconazole, could help preserve this agent for those patients who absolutely need it and hence limit the rates of breakthrough IMI, associated side effects and drug-drug interactions and decrease associated costs. This becomes even more pertinent, when considering the important variability of posaconazole blood concentrations requiring frequent dose adjustments and close TDM (146).

Objectives

Considering the -as above- described attained progress in the management of IA in hematological patients, the primary objective of this work is to discuss the current landscape and limitations of the available antifungal treatment and prophylaxis options. More specifically, the improved overall survival in allogeneic HCT recipients infected with IA in the post-voriconazole era along with the nephrotoxicity and hepatotoxicity associated with this agent, and the additional options of isavuconazole and posaconazole will be discussed.

RESULTS

Improved survival in invasive aspergillosis (Appendix 1)

Introduction

A diagnosis of IA in high-risk hematology patients was associated with high rates of mortality, up to 80-90% (25). But until the early 2000s most relevant data were coming from single-center retrospective cohort studies (1, 2, 25, 26). The Prospective Antifungal Therapy (PATH) Alliance registry was an industry-sponsored, prospectively maintained, multicenter, observational registry of patients with IFI reported by 25 major tertiary-care institutions in North America (23 in the United States of America and 2 in Canada) (147). Between 2004 and 2008, 6'845 eligible patients with IFIs were enrolled in this database (14, 28, 148-152). Using the PATH Alliance database, we performed a retrospective interim analysis to describe the epidemiology and outcomes of IFIs in autologous and allogeneic HCT recipients with IFIs (28). All adult HCT recipients with a proven or probable IFI enrolled in the PATH Alliance registry between 2004 and 2007 were included in this study. The objectives of this study were to describe the epidemiology and outcomes of IFI in HCT recipients.

Results

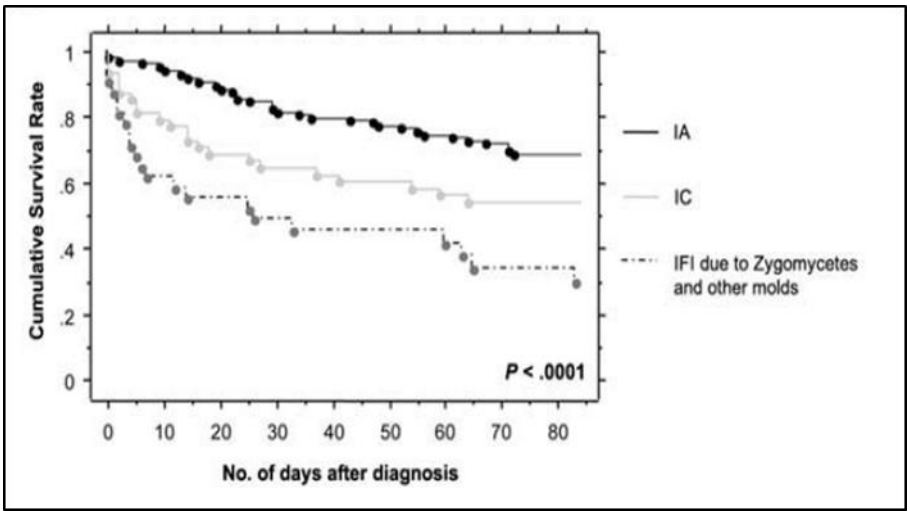
A total of 234 adult HCT recipients (73 and 161 autologous and allogeneic, respectively) with 250 proven or probable IFIs reported by 16 different institutions were included. Invasive aspergillosis was the most frequent IFI (148, 59.2%), followed by invasive candidiasis (62, 24.8%) and mucormycosis (18, 7.2%). More than 50% of IA diagnosis was made based on a non-culture test, mainly a GM EIA. More than 75% of cases of invasive candidiasis were due to non-*albicans Candida* spp. Infections due to other-than-*Aspergillus* molds occurred later (median: 173 days) post-HCT when compared to IA (median: 83 days). Overall, 6-week and 12-week mortality post-IFI diagnosis was significantly lower in patients with IA (21.5% and 35.5%, respectively) when compared to other types of IFI (P-value<0.001; **Figure 1**).

Discussion

The major finding of this study was that IA was the most commonly identified IFI in HCT recipients in the early 2000s and that associated mortality could be as low as 21.5% at 6-weeks after diagnosis. In fact, this study was the first to show that –outside of the context of a clinical trial, survival outcomes in high-risk patients with IA have significantly improved. In fact, the reported mortality of 21% at 6-weeks and 35% at 12-weeks post IA-diagnosis were consistent with the results of the pivotal clinical trial which validated voriconazole as the standard of care for the treatment of IA (75). In addition, this study showed that clinical outcomes remain dismal for patients with invasive candidiasis or with IFIs due to non-*Aspergillus* molds, including the *Mucorales*.

Figure 1. 12-week survival for HCT recipients with invasive aspergillosis, invasive candidiasis and an invasive fungal infection due to *Mucorales* and other molds. The P-value was calculated by the log-rank test.

IA: invasive aspergillosis, IC: invasive candidiasis, IFI: invasive fungal infection.



Adapted from (28)

Voriconazole and nephrotoxicity (Appendix 2)

Introduction

Patients with IA requiring treatment with voriconazole are –in their vast majority- severely immunocompromised and frequently require IV administration of their treatment, either because of the severity of their infection or because of their inability to take and adequately absorb PO medications. As already discussed, the IV formulation of voriconazole requires co-administration with SBECD. The latter has been associated with renal toxicity, mainly when administered in much higher than human doses in animal models (102, 153-155). Nevertheless, and despite the lack of relevant human data, administration of IV voriconazole is contraindicated in patients with a creatinine clearance <50mL/min. As allogeneic HCT recipients may already have a degree of renal impairment due to a myriad of other reasons, this may pose significant problems, when treatment with IV voriconazole is required.

Hence, there is a need to better study the potential nephrotoxic effect of IV voriconazole. We hypothesized that administration of IV voriconazole is well-tolerated in patients with an already existing underlying renal impairment. We then performed a 2-center, observational, retrospective study initiated at the Johns Hopkins University Hospital with the primary objective to describe the frequency of renal function deterioration in patients treated with IV voriconazole (103). We included

three different patient categories: patients with abnormal (creatinine clearance <50mL/min) baseline renal function treated with IV voriconazole (Group 1), patients with abnormal (creatinine clearance <50mL/min) baseline renal function treated with PO voriconazole (Group 2) and patients with normal (creatinine clearance ≥50mL/min) baseline renal function treated with IV voriconazole (Group 3). Using the RIFLE criteria, renal impairment was defined as any increase in serum creatinine by ≥1.5 times the baseline and/or any decrease in creatinine clearance by ≥25% (156).

Results

After screening 1096 patients at the Johns Hopkins University Hospital and the University Hospital of Pittsburgh, we included 166 patients, with 42, 47 and 77 patients attributed to Groups 1, 2, and 3, respectively. There was no significant change in mean creatinine values in none of the three groups between baseline, day 3 and by end of treatment (**Figure 2**). Using the RIFLE criteria, 19 (11.4%), 14 (8.4%) and 28 (16.9%) patients developed renal function impairment on days 3, 7, and by the end of treatment of voriconazole, respectively. Logistic regression demonstrated co-administration of penicillin-drugs as a significant predictor of renal dysfunction by the end of treatment with an odds ratio (OR) of 2.39 (95% confidence intervals, CI, 1.01, 5.66; P-value: 0.04) (**Table 1**). By day 7 of voriconazole treatment administration, only baseline liver impairment was identified as a significant predictor of renal dysfunction (OR: 5.30, 95%CI. 1.69. 16.52; P-value: 0.004). Finally, by day 3 of voriconazole administration, a history of hematologic malignancy (OR: 5.09, 95%CI, 1.38, 18.73, P-value: 0.01), fluconazole administration within 30 days prior to voriconazole (OR: 6.21, 95%CI, 1.24, 30.05, P-value: 0.03) and immunosuppressive agent co-administration (OR: 7.00, 95%CI, 2.02, 24.28, P-value: 0.002) were identified as predictors of renal dysfunction. Classification tree analysis demonstrated similar findings. Baseline renal function and mode of voriconazole administration were not found to be significant predictors of renal dysfunction.

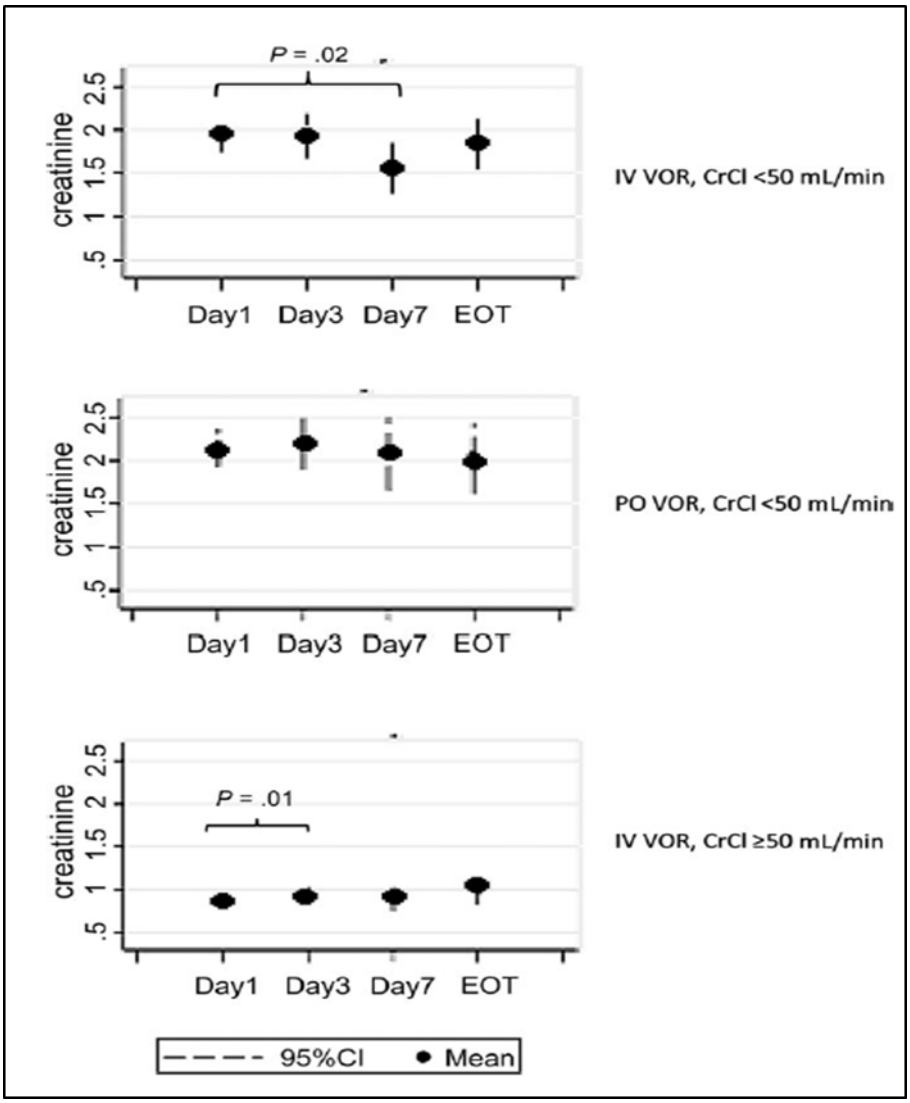
Discussion

This study confirmed our hypothesis that administration of IV voriconazole in patients with already existing renal impairment does further worsen their renal function. In contrast, other variables, including prior administration of fluconazole or concomitant administration of penicillin and immunosuppressive drugs were the most important predictors of renal function deterioration. Although not definitive, and with the major limitation of a retrospective observational study, our results were the first to address the question of renal safety of IV voriconazole in patients with creatinine clearance <50mL/min. Based on these findings, and with additional data required, IV voriconazole may potentially be administered in those patients who cannot take or absorb PO voriconazole.

Figure 2. Creatinine values for the three different groups of patients based on their baseline renal function and mode of voriconazole administration.

Only the significant P-values are depicted.

IV, intravenous. VOR, voriconazole. CrCl, creatinine clearance. PO, oral. EOT, end of treatment.



Adapted from (103)

Table 1. Risk factors for renal dysfunction by days 3, 7, and end of treatment of voriconazole administration among 166 patients treated with voriconazole with available data.

	Day 3		Day 7		End of Treatment	
Predictor	Odds Ratio	*P* Value	Odds Ratio	*P* Value	Odds Ratio	*P* Value
Ethnicity, white vs non-white	NS	NS	NS	NS	0.36	0.04
Hematologic malignancy	5.09	0.01	NS	NS	NS	NS
Fluconazole (within 30 days prior to VOR)	6.21	0.008	NS	NS	NS	NS
Baseline liver impairment[b]	NS	NS	5.30	0.004	NS	NS
Duration of VOR administration, > vs ≤7 days	0.19	0.01	NS	NS	NS	NS
Penicillins	6.12	0.03	NS	NS	2.39	0.04
Immunosuppressive agents	7.00	0.002	NS	NS	NS	NS
Vasopressive agents	0.13	0.02	NS	NS	NS	NS

Abbreviations: NS, not significant; VOR, voriconazole.

[a] Only variables with a $P < .20$ in univariate analyses were introduced in the multivariate analysis models.

[b] Defined as any of the following: aspartate aminotransferase or alanine aminotransferase >3 times the upper normal limit and/or alkaline phosphatase >2 times the upper normal limit.

Adapted from (103)

Voriconazole hepatotoxicity & early discontinuation (Appendix 3)

Introduction

Although commonly used for the treatment and prophylaxis of IFIs, voriconazole has been associated with a large number of drug-drug interactions and adverse events. As a result, many are the times that clinicians are forced to discontinue this agent, due to one or more potentially associated toxicities (82). To better describe the rate and reasons of voriconazole discontinuation in allogeneic HCT recipients, we performed an observational, retrospective, single-center cohort study including adult patients who received voriconazole as primary antifungal prophylaxis for an allogeneic HCT between 2014 and 2016 at the Memorial Sloan Kettering Cancer Center (104).

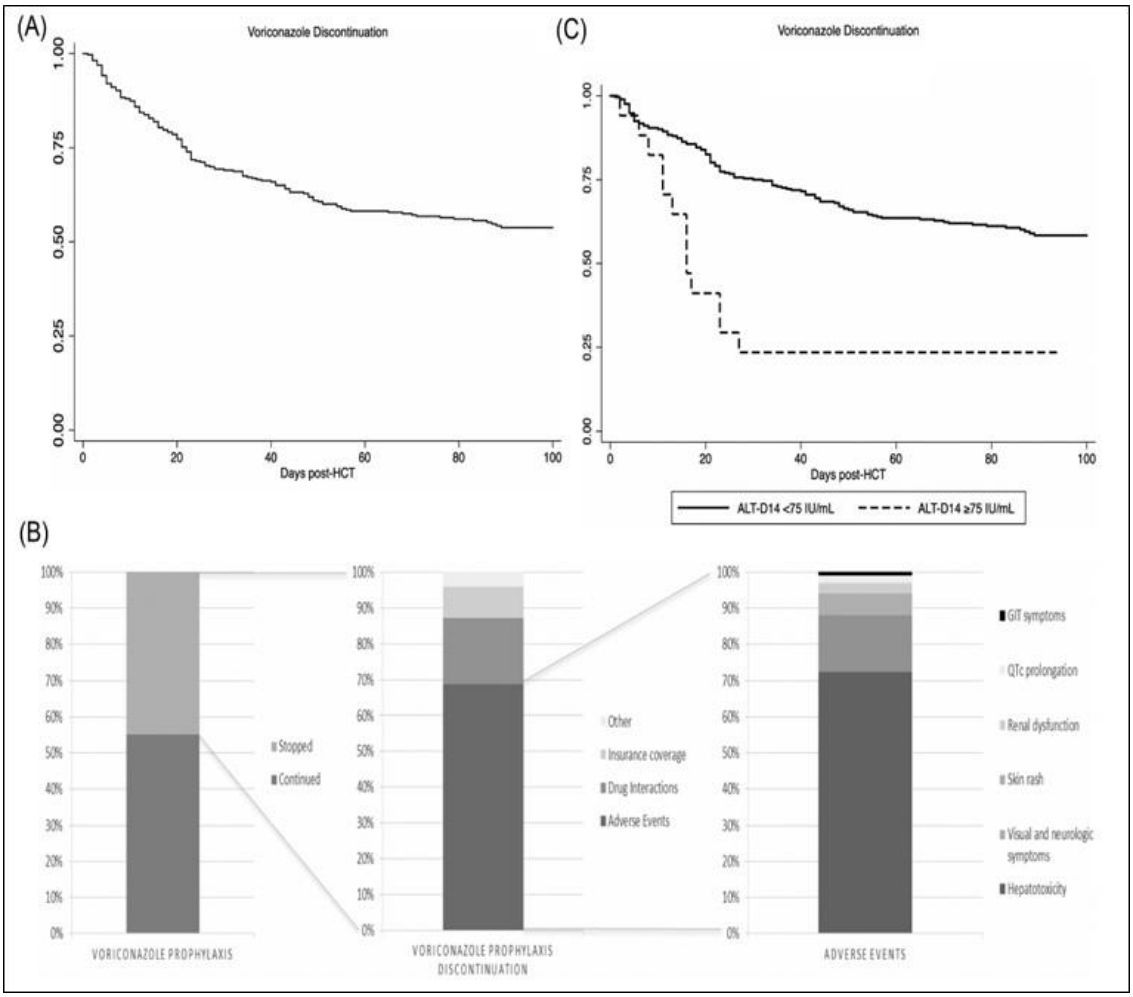
Results

Among 327 allogeneic HCT recipients who received primary antifungal prophylaxis with voriconazole, prophylaxis was started at a median of 7 days and continued for a median of 69 days. Overall, 180 (55%) patients continued voriconazole prophylaxis as per institutional protocol, while 147 (45%) patients had their prophylaxis prematurely discontinued for a number of reasons (**Figure 3**). In more detail, voriconazole was prematurely discontinued due to a potential adverse event in 101 (68.7%) patients, followed by drug-drug interactions in 27 (18.4%) patients, and other reasons in 6 (4.1%) patients. Amongst 101 patients with adverse events, voriconazole was stopped due to hepatotoxicity, visual hallucinations and neurological symptoms, skin rash, renal dysfunction, and other reasons in 73 (72.3%), 16 (15.8%), 6 (5.9%), 3 (3%), and 3 (3%) patients, respectively. Notably,

and despite the relatively high frequency of discontinuation due to liver function test abnormalities, transaminases were only moderately elevated, with only 39 (12.1%) patients having an alanine aminotransferase ≥100 IU/mL and 27 (8.4%) patients an aspartate aminotransferase ≥100 IU/mL.

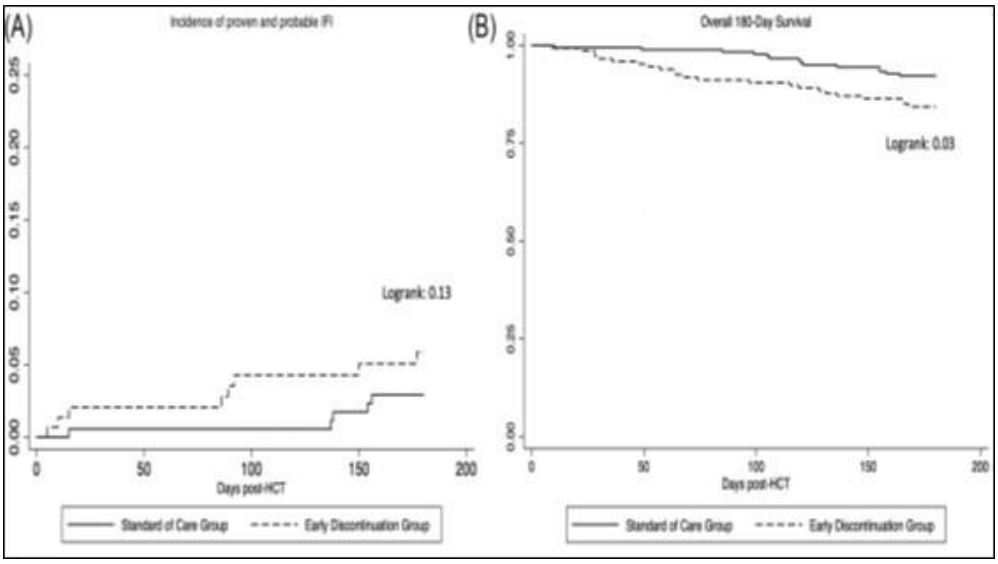
There was a trend for higher incidence of proven and probable IFI in the patient group with premature voriconazole discontinuation (5.4% vs 2.8%, P-value: 0.13; **Figure 4a**). Notably, more patients in the early-discontinuation group (23, 15.6%) died by 180 days post-HCT when compared to patients who continued voriconazole prophylaxis as per standard of care (14, 7.8%, log-rank: 0.03; **Figure 4b**).

Figure 3. Voriconazole discontinuation in a cohort of allogeneic hematopoietic cell transplant recipients overall (A) and based on alanine aminotransferase levels on day 14 of voriconazole administration (B). Presentation of reasons for premature voriconazole discontinuation (C).



Adapted from (104)

Figure 4. (A) Incidence of invasive fungal infections in allogeneic hematopoietic cell transplant recipients who remained on voriconazole ("standard of care group") versus those who had voriconazole prophylaxis prematurely discontinued ("early discontinuation group").
(B) All-cause 180-post-HCT-day mortality between allogeneic hematopoietic cell transplant recipients who remained on voriconazole ("standard of care group") versus those who had voriconazole prophylaxis prematurely discontinued ("early discontinuation group").



Adapted from (104)

Discussion

This study demonstrates a major problem associated with voriconazole administration, which is the premature discontinuation of this agent. Despite its established efficacy, voriconazole has been associated with a large number of toxicities and other potential problems, identified and better described through years of clinical experience. We have now appreciated that this agent is not feasible to be continued in a significant number of patients, due to either associated adverse events, drug-drug interactions, or other reasons. Our study was one of the few to demonstrate the significance and frequency of this problem. Despite the fact that a high-degree hepatotoxicity was not demonstrated in this study, our data suggest that clinicians are willing to discontinue voriconazole, even without a strong conviction that liver function impairment is due to this agent and much sooner before a significant hepatotoxicity is documented.

The trend for more IFI and higher mortality rates in the premature discontinuation group are hard to interpret, particularly since this study was not powered, neither designed to shed more light on

those very questions. Nevertheless, it points out to the clinical significance and importance of toxicities and medication changes in high-risk patients.

Isavuconazole: effective and safe treatment for invasive aspergillosis (Appendix 4)

Introduction

Considering the relatively high incidence of IMI with high associated morbidity and mortality and the limitations of the available treatment options, effective and safe treatments are still required. Considering its broad antifungal spectrum and favorable side-effect profile, isavuconazole was compared head-to-head to voriconazole in a phase 3, randomized, double-blind, international, multicenter, non-inferiority clinical trial as primary treatment of IA and IFIs due to non-*Aspergillus* molds, excluding *Mucorales* (77, 105, 106). Patients were randomized to either isavuconazole or voriconazole 1:1 and stratified by three additional factors: geographical region, allogeneic HCT, and malignancy stage at study entry. The primary endpoint was all-cause mortality by day 42 from study drug initiation in the intention to treat (ITT) population. The following secondary endpoints were also addressed: all-cause mortality by day 84, overall, clinical, mycological and radiological response by days 42 and 84 in the ITT and modified ITT (mITT) patient populations, and safety and tolerability (77).

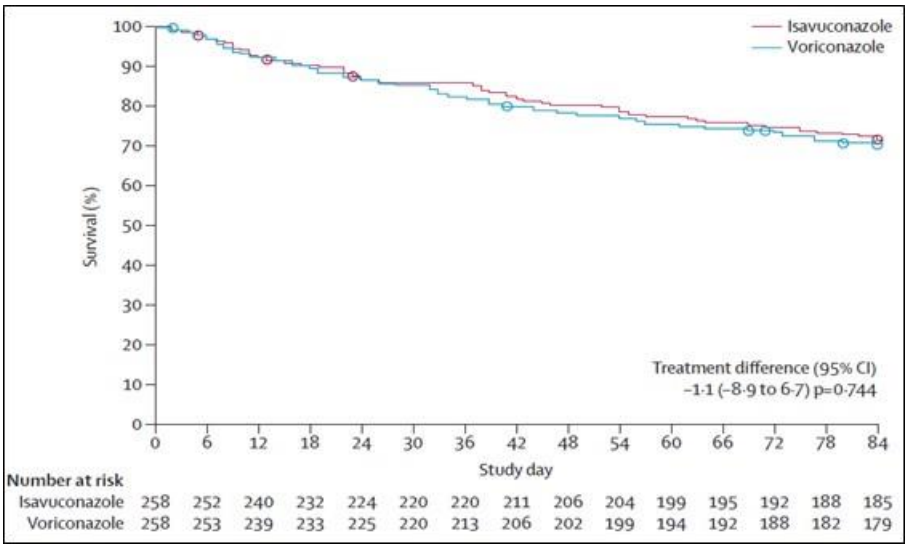
Results

A total of 527 patients were randomized, with 258 patients finally assigned to the ITT for each group. The mITT population, defined as patients with a proven or probable IMI, included 143 and 129 patients for the isavuconazole and voriconazole group, respectively. The mycological ITT (myITT) population included 123 and 108 patients with proven or probable IA in the isavuconazole and voriconazole groups, respectively. All-cause mortality at day 42 in the ITT population was 19% and 20% for isavuconazole and voriconazole, respectively (adjusted treatment difference, 95%CI: -1.0%, -7.8, 5.7) (**Figure 5**). Hence, the study met the primary objective to demonstrate non-inferiority of isavuconazole when compared to voriconazole for primary treatment of IMI. Day 84 all-cause mortality in the ITT population was 29% and 31% for isavuconazole and voriconazole, respectively (adjusted treatment difference, 95%CI: -1.4%, -9.2, 6.3). Similar findings were observed for the mITT and myITT patient populations. For the mITT population, 42-day all-cause mortality was 20% and 23% for isavuconazole and voriconazole, respectively (adjusted treatment difference, 95%CI: -2.6%, -12.2, 6.9). Similarly, 84-day all-cause mortality was 30% and 37% for isavuconazole and voriconazole, respectively (adjusted treatment difference, 95%CI: -5.5%, -16.1, 5.1). For the myITT population, 42-day all-cause mortality was 17% and 18% for isavuconazole and voriconazole, respectively (adjusted treatment difference, 95%CI: -2.7%, -12.9, 7.5). Similarly, 84-day all-cause mortality was 28% and

36% for isavuconazole and voriconazole, respectively (adjusted treatment difference, 95%CI: -5.7, -17.1, 5.6).

In terms of safety, isavuconazole was associated with significantly lower rates of hepatotoxicity compared to voriconazole (9% versus 16%, P-value: 0.016), skin and subcutaneous tissue disorders (33% versus 42%, P-value: 0.037) and eye disorders (15% versus 27%, P-value: 0.002).

Figure 5. 84-day overall survival of patients with an invasive mold infection treated with isavuconazole and voriconazole. Day 0 represents the first day of drug administration.



Adapted from (77).

Discussion

In this randomized double-blind multi-center study, we demonstrated that isavuconazole was non-inferior to voriconazole for the primary treatment of IMI, including IA, albeit with a toxicity profile more favorable than that of voriconazole. Based on this registration clinical trial, isavuconazole is currently considered as first-line treatment for IA based on consensus European guidelines (79). Notably, all-cause mortality by day-42 and day-84 in this trial were comparable to those observed in prior clinical trials, comparing voriconazole to amphotericin-B deoxycholate and voriconazole versus voriconazole with anidulafungin combination therapy (75).

Posaconazole level variability and toxicities (Appendix 5)

Introduction

Posaconazole has been validated and established as the standard of care for primary antifungal prophylaxis in patients with acute myelogenous leukemia with anticipated neutropenia for ≥14 days

and allogeneic HCT recipients with GvHD requiring treatment with corticosteroids at ≥1mg/kg/day (125-127). However, administration of posaconazole is hindered due to a variety of reasons, including, but not limited to, significant drug-drug interactions, hepatotoxicity, associated costs, and erratic blood concentrations.

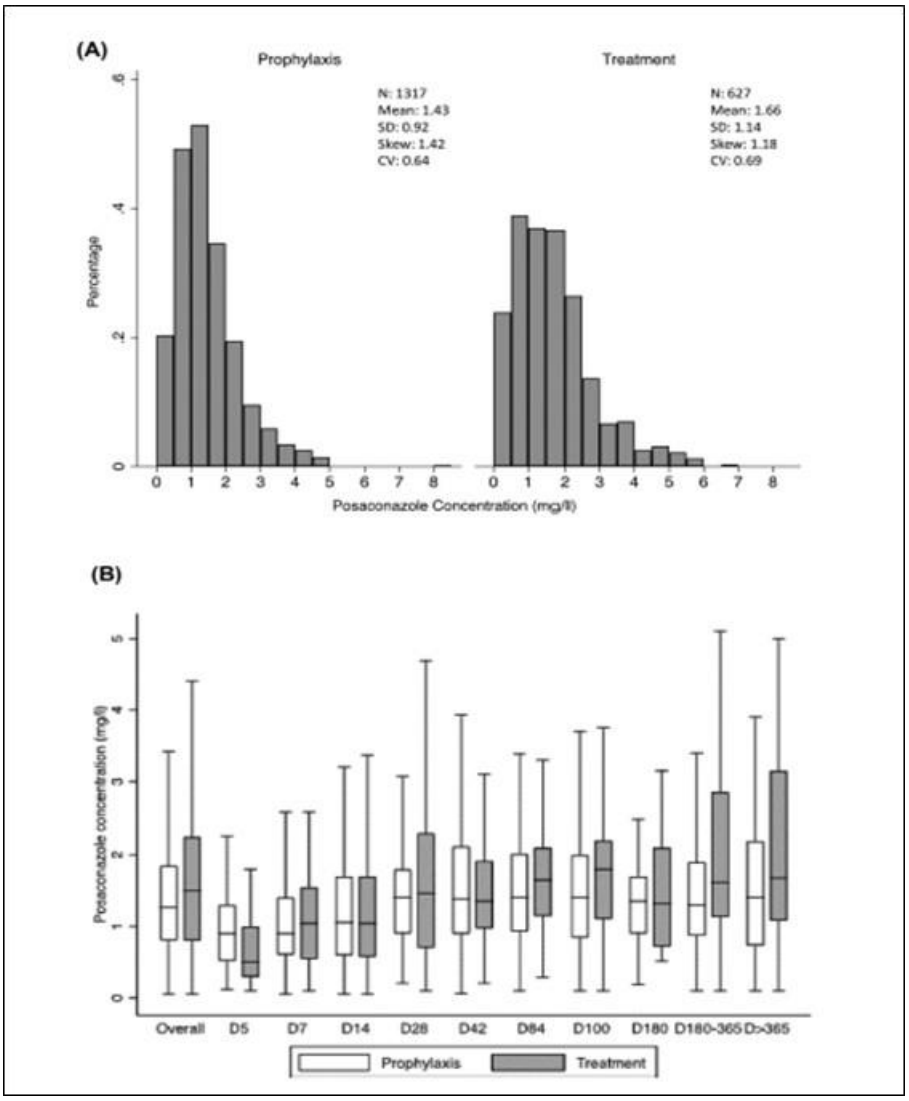
Posaconazole blood level targets have been proposed by relevant expert guidelines at ≥0.7 mg/L and ≥1.0 mg/L for prophylaxis and treatment, respectively (79, 157). To better understand the distribution and variability of posaconazole blood concentrations, we performed a retrospective, cohort study within the context of the Swiss Transplant Cohort Study (STCS) (146). All adult allogeneic HCT recipients included in the STCS cohort between 2016 and 2018 who received posaconazole as prophylaxis and/or treatment were included. Patients were identified through the STCS and hospital/pharmacy databases at the three major university hospitals performing allogeneic HCT in Switzerland. The primary objective of this study was to describe the posaconazole concentrations. Secondary objectives included the identification of predictors of therapeutic posaconazole levels, possible associations between posaconazole dosing, blood concentrations and hepatotoxicity, and the description of breakthrough IMI in patients receiving posaconazole.

Results

In a total of 288 allogeneic HCT recipients, 194 (67.4%) and 94 (32.6%) patients received posaconazole as prophylaxis and treatment, respectively. Only 160 (55.6%) patients received a loading posaconazole dose. Overall, there were 1’944 posaconazole level measurements during the study period, with a median of 5 tests per patient. The median posaconazole level in the study was 1.3 mg/L (interquartile range, IQR: 0.8, 1.96) with large intra- (57.0%) and inter-individual (65.0%) variability (**Figure 6**). Notably, posaconazole level was <0.7 mg/L and <1.0 mg/L in 19.7% and 33.7% of samples tested, respectively. Among patients who received posaconazole as prophylaxis, 19.7% samples were <0.7 mg/L, while 31.4% tests in patients treated with posaconazole had a level <1.0 mg/L. While the vast majority of patients (268, 93.1%) received 300mg once daily as initial maintenance dose at baseline, by the end of treatment there was a large variability in the posaconazole doses administered, from 100mg to 1000mg once daily (**Figure 7**). Overall, 176 (61.1%) patients required at least one dose or formulation change during their treatment course. Nine (3.1%) breakthrough IFI were diagnosed during the study period. There was no difference in the mean posaconazole level between patients with (1.32 mg/L) and without (1.4 mg/L, P-value: 0.55) breakthrough IFI, with a median posaconazole level amongst the 9 patients with a breakthrough infection at 1.31 mg/L (range: 0.4, 1.68). Except for one patient with a posaconazole level at 0.4 mg/L

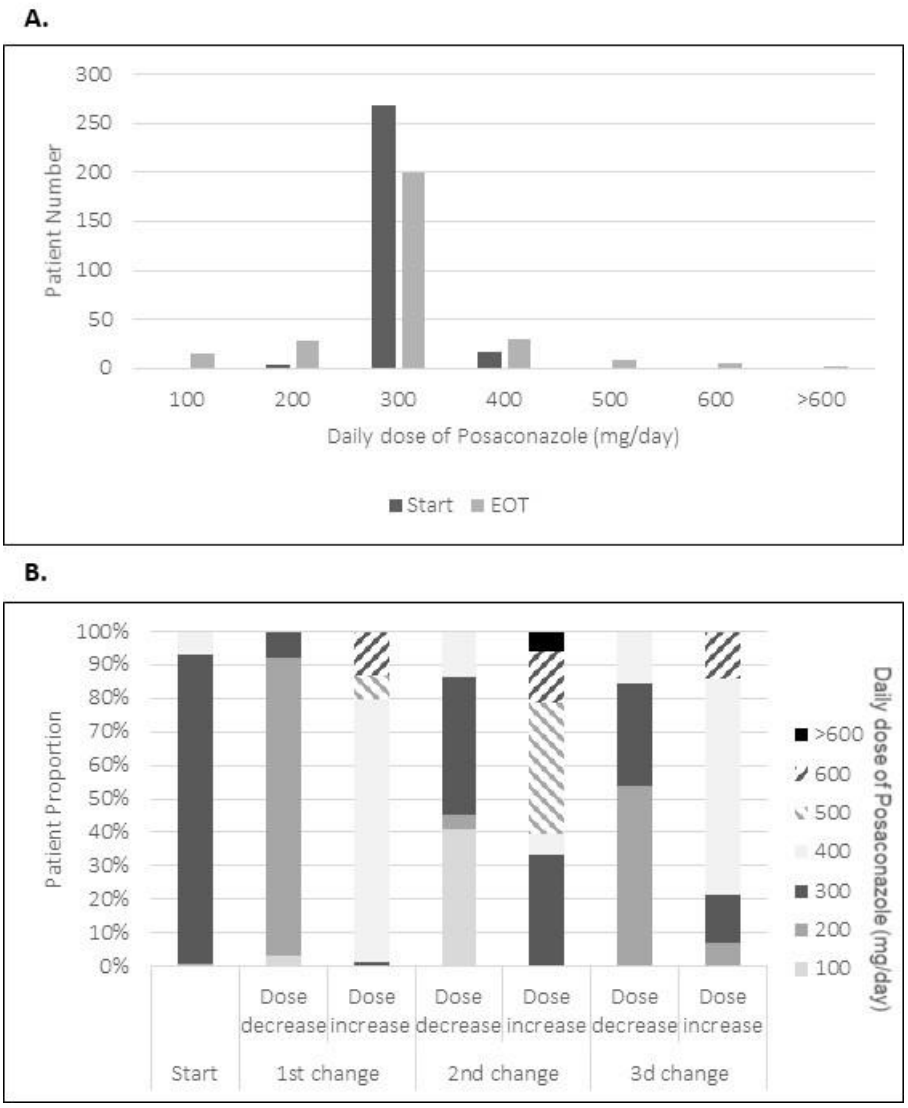
measured at 9 days prior to their breakthrough infection, all other patients had a posaconazole level >0.95 mg/L before their breakthrough infection was diagnosed.

Figure 6. Distribution of posaconazole blood concentrations in patients who received this agent as prophylaxis and treatment presented as histograms (A) and blox-plots (B).



Adapted from (146)

Figure 7. (A) Distribution of posaconazole daily dose at treatment initiation and by end-of-treatment for all patients. (B) Posaconazole daily dose distribution in 155 patients with at least one dose change during their treatment (only data for the first 3 changes are presented).



Adapted from (146)

Discussion

Despite its retrospective nature and other limitations, this study clearly demonstrated the large variability of posaconazole blood concentrations in a large contemporary cohort of allogeneic HCT recipients. One in 3 to 4 patients had posaconazole concentrations below the proposed target. Nevertheless, the rate of breakthrough infections remained very low and did not seem to be associated with the observed blood concentrations of posaconazole.

Based on our observations, it is unclear whether posaconazole TDM is necessary and whether it should be routinely and universally performed. In addition, the limitations of posaconazole, particularly when it comes to the large variability of blood concentrations amongst patients treated with this agent, may additionally hinder the optimal utilization of this agent.

CONCLUSIONS

Significant improvement in overall survival in patients with IA has been demonstrated in the post-voriconazole era. Although our and other data suggest that voriconazole may be an effective agent, its use may be limited due to associated toxicities and drug-drug interactions in a -much underappreciated in the past- large number of patients. The available alternatives, including isavuconazole and posaconazole, have been shown to be non-inferior to voriconazole albeit with more favorable toxicity-profiles.

The problems associated with voriconazole administration have been well known and described in the literature during the last two decades. However, their real impact on clinical practice has been poorly described. Based on our observations, voriconazole may be discontinued in up to 40-45% of allogeneic HCT recipients, who receive this agent as primary antifungal prophylaxis. This is an extraordinarily high rate of discontinuation, suggesting that an alternative option may be required in up to 1 in 2 patients on voriconazole antifungal prophylaxis. Notably, our data did not include patients who receive voriconazole as primary treatment for IA. In this latter group of patients, the threshold to stop the administered treatment may be much higher. However, our data clearly show that we may not always be able to continue and administer voriconazole in a significant number of patients that need this treatment.

Additional options exist, with isavuconazole and posaconazole representing effective and safe treatments for IA. Isavuconazole was found non-inferior and better tolerated than voriconazole. It has the advantage to not require co-administration with cyclodextrin. Furthermore, its effect on the QTc interval may facilitate antifungal treatment in patients with prolonged QTc interval and co-administration with other QTc-prolonging agents. Moreover, isavuconazole is only a moderate CYP3A4 inhibitor, therefore with fewer drug-drug interactions than voriconazole or even posaconazole, both strong inhibitors of this CYP. All in all, isavuconazole represents an excellent treatment alternative, particularly in those patients who may not be able to tolerate voriconazole.

Similarly, posaconazole was recently shown to be non-inferior to voriconazole for the treatment of IA, also with a more favorable side effect profile. Fewer hepatotoxicity, eye, skin and neurological events were observed in patients treated with posaconazole versus voriconazole. However, posaconazole use may be hindered by the large variability of blood concentrations observed and the important drug-drug interactions, as a result of its complex metabolism. Our data showing significant variability in posaconazole blood concentrations and requirement for dose changes in more than half

of patients receiving this agent suggest that close patient monitoring may be required. As most treatment with posaconazole is administered on an outpatient basis, this is an important consideration for clinicians and the follow-up of those patients.

Considering the above, it is evident that none of the available treatments for IA has an optimal toxicity and drug-drug interaction profile. Moreover, the existing data suggest that all-cause 6- and 12-week mortality in patients with IA have remained in the range of 20% and 35%, respectively, since the early 2000s, when the results of the pivotal clinical trial of voriconazole compared to conventional amphotericin-B were reported (75). Notably, upon review of the mortality rates reported in the major clinical trials for the treatment of IA since 2002, excluding patients treated with amphotericin-B deoxycholate in the voriconazole registration trial, we can appreciate that they have remained in the same range during the last two decades (**Table 2**). More specifically, 6- and 12-week all-cause post antifungal treatment initiation for IA has ranged between 19-30% (median: 19.75 %) and 28-41% (median: 32.5%), respectively. In other words, 1 in 5 and 1 in 3 patients with IA are still likely to die by 42 and 84 days after appropriate targeted antifungal treatment initiation.

The fact that 12-week survival in patients with IA has remained in the range of 25 and 35% for the last two decades, despite the progress attained in the fields of diagnostics and therapeutics, remains to be further studied and analyzed. It is true that since the 1990s, the approaches in the field of Hematology and Bone Marrow Transplantation have significantly changed. Conditioning regimens have been adjusted to include reduced intensity and non-myeloablative regimens. Stem cells may come from bone marrow, peripheral blood stem cells or cord blood and be T-cell depleted or not. Haplo-identical or mis-matched unrelated donors are more commonly used. Similarly, older and higher-risk patients are more frequently accepted for an allogeneic HCT as well. Additional immunosuppressive and chemotherapeutic strategies to prevent GvHD and/or post-HCT relapse are applied more and more in clinical practice. The above suggest that allogeneic HCT recipients today may not necessarily resemble the patient population transplanted in the 1980 and 1990s. Higher-risk patients and higher-risk HCT techniques might have impacted on the overall immune status of allogeneic HCT recipients in the 2020s, and also their susceptibility to IFIs, including IA, with eventually more severe clinical presentations and dismal clinical outcomes.

Table 2. Clinical efficacy data among patients with invasive aspergillosis between 2000 and 2020.

Ref[1]	6-week mortality		12-week mortality		12-week clinical response	
(75)[2]	VCZ: 20%	AMB-d: 35%	VCZ: 29.2%	AMB-d: 42.1%	VCZ: 52.8%	AMB-d: 31.6%
(28)[3]	20%		35.5%		63.5%	
(74)[4]	LAMB-3mg: 19%	LAMB-10mg: 30%	LAMB-3mg: 28%	LAMB-10mg: 41%	LAMB-3mg: 50%	LAMB-10mg: 46%
(101)[5]	VCZ: 27.8%	VCZ+ANI: 19.5%	VCZ: 39.4%	VCZ+ANI: 29.3%	VCZ: 43%	VCZ+ANI: 32.6%
(77)[6]	VCZ: 22%	ICZ: 19%	VCZ: 36%	ICZ: 28%	VCZ: 36%	ICZ: 35%
(78)[7]	VCZ: 19%	PCZ: 19%	VCZ: 31%	PCZ: 34%	VCZ: 46%	PCZ: 42%
Mean/Median (Range; SD)[8]	21.45 / 19.75 (19, 30; 3.9)		33.14 / 32.5 (28, 41; 4.7)		44.69 / 44.5 (32.6, 63.5; 9.3)	

Ref: Reference, VCZ: Voriconazole, AMB-d: Amphotericin-B deoxycholate, LAMB-3mg: Liposomal Amphotericin-B 3mg/kg/day, LAMB-10mg: Liposomal Amphotericin-B 10mg/kg/day, ANI: Anidulafungin, ICZ: Isavuconazole, PCZ: Posaconazole, SD: Standard Deviation.

[1] In chronological order of publication. 12-week clinical response outcomes include complete and partial response.

[2] Mortality and complete and partial response were reported on the modified intention-to-treat population.

[3] Results are presented for the overall hematopoietic cell transplant recipients with a diagnosis of proven and probable invasive aspergillosis.

[4] This study compared liposomal amphotericin-B at a standard dose of 3mg/kg/day to a high-dose 10mg/kg/day. Results are presented for the modified intention-to-treat population, defined as patients with a confirmed diagnosis of an invasive mold infection by the Data and Safety Review Committee. Results were similar for 103 and 92 patients with a diagnosis of invasive aspergillosis in the standard and high-dose groups, respectively.

[5] Results are presented for the modified intention-to-treat population, defined as patients with proven or probable invasive aspergillosis. Complete and partial response rates are presented at 6 weeks post study enrollment.

[6] Results are presented for the mycological intention-to-treat patient population, defined as patients with proven or probable invasive aspergillosis. Complete and partial response were reported at the end-of-treatment.

[7] Results are presented for the full analysis set population, defined as patients with proven and probable invasive aspergillosis.

[8] Mean and median calculated for all studies and agents used, excluding the values for the group treated with AMB-d.

In parallel to the above, significant progress has been achieved in the field of infectious diseases, as discussed in detail in the Introduction of this work. Better diagnostic tests and better understanding of the pathophysiology of HCT and IFI, including the identification of important and reliable risk factors, have enabled clinicians to accurately and promptly make the diagnosis of IA and start antifungal treatment. In addition, routine antifungal prophylaxis is applied in most centers, further impacting the incidence of IA and other IMIs.

Hence, it is likely that despite the progress attained in the fields of infectious diseases and hematology / HCT, clinical outcomes in patients with IA might have stagnated during the last two decades due to the fact that patients are significantly sicker and with more comorbidities than before. Whether the existing gap of 20-30% in all-cause mortality may be further decreased remains to be discussed. While the "host-effect" may not always be measured or accounted for, it is important to reflect on whether newer and better diagnostic and/or therapeutic interventions may further impact clinical outcomes. Notably, with broad-spectrum azoles appear to have reached a plateau in terms of clinical outcomes and no additional therapeutic benefit may be expected from this class of agents, despite their differences in terms of toxicities and drug-drug interactions.

No new antifungal agent classes have been introduced in clinical practices since echinocandins in the early 2000s. Isavuconazole was the last new antifungal agent to be introduced in clinical practice in the last decade. This may change in the near future, with newer antifungal options already in phase 2-3 clinical trials showing promising results (**Table 3**) (158, 159). For instance, a new formulation of orally administered itraconazole, SUBA-itraconazole, is under investigation. Itraconazole is administered within a pH-dependent polymer matrix, which significantly improves its absorption with an estimated oral bioavailability of 173%. The first orally administered formulation of amphotericin-B is under investigation, with the compound delivered in a multi-layered spiral cochleate structure, thus allowing oral absorption and delivery to infected tissues. A new generation echinocandin, rezafungin, is in phase 3 clinical trials for the treatment of invasive candidiasis and as primary antifungal prophylaxis in allogeneic HCT recipients. While not significantly different from anidulafungin, this agent has a long half-life, allowing once weekly administration and better concentrations in the tissues, including the lungs.

While promising and exiting, all the above-mentioned new antifungal agents belong to the already existing classes of triazoles, polyenes, and echinocandins, respectively. However, for the first time after many decades, new classes of antifungals are under consideration (**Table 3**). Some of those new agents / classes appear to have excellent activity against most *Aspergillus* species and favorable

pharmacokinetic and toxicity profiles. Their efficacy has not, as yet, been compared to the standard of care (voriconazole or isavuconazole).

Ibrexafungerp is a glucan synthase inhibitor, targeting the synthesis of fungal cell wall, with a broad spectrum of activity including *Candida* spp. (including *C. auris*) and *Aspergillus* spp., *Pneumocystis* spp., *Paecilomyces variotii* and *Lomentospora prolificans* (160, 161). Despite its highly-protein bound properties, it can penetrate and distribute very well in most tissues, excluding the brain (162). In fact, concentrations as high as 100 times serum concentration have been described in infected necrotic liver tissue (162). Ibrexafungerp is available in both IV and PO formulations and does not appear to significantly interact with CYP 3A4, 2C19, or 2C9; it is a mild inhibitor of CYP2C8 (160, 163, 164). Olorofim is a first in class (orotomides) new antifungal agent with an intracellular target (165, 166). This compound inhibits the synthesis of pyrimidine, by inhibiting an enzyme important for this process, the dihydroorotate dehydrogenase (DHODH) (165, 166). Its spectrum of activity includes most molds, including *Aspergillus* spp., *Fusarium* spp., *Lomentospora prolificans* and dimorphic fungi (167-169). It has no activity against *Candida* spp., *Cryptococcus* spp., and *Mucorales*. It has minimal toxicities, considering its specific fungal target, is a weak CYP3A4 inhibitor and may be administered PO (165, 166). Fosmanogepix targets the enzyme Gwt1, necessary for the synthesis of glycosylphosphatidylinositol (GPI), a protein necessary for the stability of the fungal cell wall (170, 171). It is available as IV and PO formulation with excellent bioavailability and a very broad spectrum of activity, including yeasts (excluding *C. krusei*), molds, and dimorphic fungi. Similat to olorofim, due to its fungal specific target, it has minimal associated toxicities. Finally, VL-2397, a cyclic exapeptide, appears to have excellent activity against *Aspergillus* and some yeasts (*Candida, Cryptococcus* and *Trichosporon*) has been removed from clinical trials, despite its excellent profile and promising efficacy data (172-174).

The above underline that new agents and new classes of antifungal agents are under investigation and development. While we do not know whether those new treatments options will be better and safer than the already existing ones, the fact that for the first time after two decades new classes of antifungal treatments may come to be added to our antifungal armamentarium holds promise in the field of IFI.

Table 3. New antifungal agents under consideration and clinical research (158, 159).

Agent	Class	Spectrum	Administration	Pharmacology	Status	Indications sought
SUBA-Itraconazole	Azoles	*Candida, Aspergillus, Coccidioides, Histoplasmsa*	PO	• Increased bioavailability	Phase 3	• Endemic mycoses • Antifungal prophylaxis (HCT)
Endocochleated Amphotericin B (MAT2203)	Polyenes	*Candida, Cryptococcus, Aspergillus, Mucorales, Coccidioides, Histoplasma*	PO	• Rapid drug uptake by fungi • Extensive tissue distribution • High liver concentrations	Phase 2	• Mucocutaneous candidiasis, • Cryptococcal meningitis • Antifungal prophylaxis
Rezafungin	Echinocandin	*Candida, Aspergillus, Pneumocystis*	IV, SC	• Concentration dependent activity • Long T1/2 (133-150hours) • Once weekly administration • Excellent tissue distribution	Phase 3	• Invasive candidiasis • Antifungal prophylaxis (HCT)
VT-1129 (VT-1161, VT-1598)	Tetrazoles	*Candida, Cryptococcus, Aspergillus, Mucorales, Coccidioides, Histoplasma, Blastomyces*	PO	• VT-1129: long T1/2 (6 days)	Phase 2	• Tinea pedis, onychomycosis • Vulvovaginal candidiasis
Ibrexafungerp	Triterpenoid	*Candida, Aspergillus, Paecilomyces variotii, Lomentospora porlificans, Pneumocystis*	PO, IV	• Excellent tissue penetration (no CNS) • Excellent bioavailability • Increased absorption with food • Modest CYP2C8 inhibitor	Phase 3	• Refractory IFI • Vulvovaginal candidiasis • *Candida auris* infections
Fosmanogepix (APX001)	GPI inhibitor	*Candida, Cryptococcus, Aspergillus, Fusarium, Scedosporium, Lomentospora porlificans, Mucorales, Coccidioides*	PO, IV	• Excellent bioavailability	Phase 2	• Invasive candidiasis • Invasive aspergillosis • Coccidiomycosis • Rare mold infections
Olorofim	Orotomides	*Aspergillus, Fusarium,*	PO	• Excellent bioavailability	Phase 2	• Difficult to treat IFI

		Scedosporium apiospermum, Lomentospora porlificans, Penicillium marneffei, Coccidioides, Histoplasma, Blastomyces		• Excellent tissue distribution • Weak CYP3A4 inhibitor		
VL-2397	Cyclic hexapeptides	*Aspergillus, Candida, Cryptococcus, Trichosporon*	IV	• Rapid and potent fungicidal activity against *Aspergillus*	None	• No on-going clinical trials

SUBA: Super-Bioavailability, PO: Oral, IV: Intravenous, SC: Subcutaneous, IFI: Invasive Fungal Infection, HCT: Hematopoietic Cell Transplant, GPI: Glycophosphatidylinositol.

In addition to the underlying host-immune status and available treatment options, genetic factors may eventually prove to be important players in the fight against IFI. A number of genetic polymorphisms have been associated with susceptibility to different infections, including IA and other IMIs (31, 33-35, 37, 175-179). For instance, pentraxin-3 (PTX3) has been shown to be a significant risk factor for IA in patients with acute myeloid leukemia, solid organ transplant and allogeneic HCT recipients (30, 32-34). The effect of genetic factors as such on clinical outcomes has not been, as yet, further studied. However, the realization that underlying genetic factors may impact clinical outcomes may open new opportunities in the field of IFIs. Identifying and stratifying patients for antifungal prophylaxis or early initiation of preemptive antifungal treatment based on genetic polymorphisms should be further studied and -if of proven efficacy- incorporated in clinical practice. For instance, an ongoing clinical trial enrolls patients with acute myelogenous leukemia who are not neutropenic upon diagnosis for antifungal prophylaxis and stratifies them based on their underlying PTX3 genetic polymorphisms to receive either posaconazole or fluconazole as primary antifungal prophylaxis (ClincalTrials.gov NCT03828773). This approach of personalized medicine may eventually gain more ground in the years to come and represents an important part of the currently ongoing translational and clinical research.

To conclude, significant progress has been attained in the management of IA in allogeneic HCT recipients, with the new generation azoles having dominated the field during the last two decades, offering viable, effective and safe treatment options. Having achieved a plateau in overall survival since the early 2000s, it is time to explore additional options, including new antifungal treatments and personalized medicine approaches, in order to further improve clinical outcomes and survival in allogeneic HCT recipients with a severe infection due to *Aspergillus* spp. and other molds.

REFERENCES

1. Marr KA, Carter RA, Boeckh M, Martin P, Corey L**.** Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood. 2002;100(13):4358-66.
2. Marr KA, Carter RA, Crippa F, Wald A, Corey L**.** Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2002;34(7):909-17.
3. Neofytos D**.** Antimicrobial Prophylaxis and Preemptive Approaches for the Prevention of Infections in the Stem Cell Transplant Recipient, with Analogies to the Hematologic Malignancy Patient. Infect Dis Clin North Am. 2019;33(2):361-80.
4. Marr KA, Seidel K, White TC, Bowden RA**.** Candidemia in allogeneic blood and marrow transplant recipients: Evolution of risk factors after the adoption of prophylactic fluconazole. Journal of Infectious Diseases. 2000;181(1):309-16.
5. Verfaillie C, Weisdorf D, Haake R, Hostetter M, Ramsay NK, McGlave P**.** Candida infections in bone marrow transplant recipients. Bone Marrow Transplant. 1991;8(3):177-84.
6. Kontoyiannis DP, Vaziri I, Hanna HA, Boktour M, Thornby J, Hachem R, et al. Risk Factors for Candida tropicalis fungemia in patients with cancer. Clin Infect Dis. 2001;33(10):1676-81.
7. Safdar A, van Rhee F, Henslee-Downey JP, Singhal S, Mehta J**.** Candida glabrata and Candida krusei fungemia after high-risk allogeneic marrow transplantation: no adverse effect of low-dose fluconazole prophylaxis on incidence and outcome. Bone Marrow Transplant. 2001;28(9):873-8.
8. Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med. 1992;326(13):845-51.
9. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation--a prospective, randomized, double-blind study. J Infect Dis. 1995;171(6):1545-52.
10. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. J Clin Oncol. 2018:JCO1800374.
11. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15(10):1143-238.
12. Marr KA**.** Invasive Candida infections: the changing epidemiology. Oncology (Williston Park). 2004;18(14 Suppl 13):9-14.

13. Chang A, Neofytos D, Horn D. Candidemia in the 21st century. Future Microbiol. 2008;3(4):463-72.
14. Pfaller M, Neofytos D, Diekema D, Azie N, Meier-Kriesche HU, Quan SP, et al. Epidemiology and outcomes of candidemia in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance(R)) registry, 2004-2008. Diagn Microbiol Infect Dis. 2012;74(4):323-31.
15. Horn DL, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis. 2009;48(12):1695-703.
16. Siwek GT, Pfaller MA, Polgreen PM, Cobb S, Hoth P, Magalheas-Silverman M, et al. Incidence of invasive aspergillosis among allogeneic hematopoietic stem cell transplant patients receiving voriconazole prophylaxis. Diagn Microbiol Infect Dis. 2006;55(3):209-12.
17. Pavie J, Lacroix C, Hermoso DG, Robin M, Ferry C, Bergeron A, et al. Breakthrough disseminated Aspergillus ustus infection in allogeneic hematopoietic stem cell transplant recipients receiving voriconazole or caspofungin prophylaxis. J Clin Microbiol. 2005;43(9):4902-4.
18. Pagano L, Gleissner B, Fianchi L. Breakthrough zygomycosis and voriconazole. J Infect Dis. 2005;192(8):1496-7; author reply 7.
19. Oren I. Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia. Clin Infect Dis. 2005;40(5):770-1.
20. Cudillo L, Girmenia C, Santilli S, Picardi A, Dentamaro T, Tendas A, et al. Breakthrough fusariosis in a patient with acute lymphoblastic leukemia receiving voriconazole prophylaxis. Clin Infect Dis. 2005;40(8):1212-3.
21. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med. 2004;350(9):950-2.
22. Kobayashi K, Kami M, Murashige N, Kishi Y, Fujisaki G, Mitamura T. Breakthrough zygomycosis during voriconazole treatment for invasive aspergillosis. Haematologica. 2004;89(11):ECR42.
23. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. Clin Infect Dis. 2004;39(5):743-6.
24. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of Aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis. 1997;175(6):1459-66.
25. Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. Clin Infect Dis. 2007;44(4):531-40.
26. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. Clin Infect Dis. 2008;47(8):1041-50.

27. Herbrecht R. Improving the outcome of invasive aspergillosis: new diagnostic tools and new therapeutic strategies. Ann Hematol. 2002;81 Suppl 2:S52-3.
28. Neofytos D, Horn D, Anaissie E, Steinbach W, Olyaei A, Fishman J, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis. 2009;48(3):265-73.
29. Sipsas NV, Kontoyiannis DP. Clinical issues regarding relapsing aspergillosis and the efficacy of secondary antifungal prophylaxis in patients with hematological malignancies. Clin Infect Dis. 2006;42(11):1584-91.
30. Brunel AS, Wojtowicz A, Lamoth F, Spertini O, Neofytos D, Calandra T, et al. Pentraxin-3 polymorphisms and invasive mold infections in acute leukemia patients with intensive chemotherapy. Haematologica. 2018.
31. Fisher CE, Hohl TM, Fan W, Storer BE, Levine DM, Zhao LP, et al. Validation of single nucleotide polymorphisms in invasive aspergillosis following hematopoietic cell transplantation. Blood. 2017;129(19):2693-701.
32. Wojtowicz A, Lecompte TD, Bibert S, Manuel O, Rueger S, Berger C, et al. PTX3 Polymorphisms and Invasive Mold Infections After Solid Organ Transplant. Clin Infect Dis. 2015;61(4):619-22.
33. Cunha C, Kurzai O, Carvalho A. PTX3 deficiency and aspergillosis. N Engl J Med. 2014;370(17):1666-7.
34. Cunha C, Aversa F, Lacerda JF, Busca A, Kurzai O, Grube M, et al. Genetic PTX3 deficiency and aspergillosis in stem-cell transplantation. N Engl J Med. 2014;370(5):421-32.
35. Lamoth F, Rubino I, Bochud PY. Immunogenetics of invasive aspergillosis. Med Mycol. 2011;49 Suppl 1:S125-36.
36. Cunha C, Di Ianni M, Bozza S, Giovannini G, Zagarella S, Zelante T, et al. Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. Blood. 2010;116(24):5394-402.
37. Bochud PY, Chien JW, Marr KA, Leisenring WM, Upton A, Janer M, et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med. 2008;359(17):1766-77.
38. Caillot D, Couaillier JF, Bernard A, Casasnovas O, Denning DW, Mannone L, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. J Clin Oncol. 2001;19(1):253-9.

39. Greene RE, Schlamm HT, Oestmann JW, Stark P, Durand C, Lortholary O, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis. 2007;44(3):373-9.

40. Greene RE, Mauskopf J, Roberts CS, Zyczynski T, Schlamm HT**.** Comparative cost-effectiveness of voriconazole and amphotericin B in treatment of invasive pulmonary aspergillosis. Am J Health Syst Pharm. 2007;64(24):2561-8.

41. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52(4):e56-93.

42. 2.2016 NGV 2016;Pageshttps://oralcancerfoundation.org/wp-content/uploads/2016/09/infections.pdf on 30 September 2018.

43. Kojima R, Tateishi U, Kami M, Murashige N, Nannya Y, Kusumi E, et al. Chest computed tomography of late invasive aspergillosis after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2005;11(7):506-11.

44. McWhinney PH, Kibbler CC, Hamon MD, Smith OP, Gandhi L, Berger LA, et al. Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: 13 years' experience. Clin Infect Dis. 1993;17(3):397-404.

45. Reichenberger F, Habicht J, Matt P, Frei R, Soler M, Bolliger CT, et al. Diagnostic yield of bronchoscopy in histologically proven invasive pulmonary aspergillosis. Bone Marrow Transplant. 1999;24(11):1195-9.

46. Levy H, Horak DA, Tegtmeier BR, Yokota SB, Forman SJ**.** The value of bronchoalveolar lavage and bronchial washings in the diagnosis of invasive pulmonary aspergillosis. Respir Med. 1992;86(3):243-8.

47. Kahn FW, Jones JM, England DM**.** The role of bronchoalveolar lavage in the diagnosis of invasive pulmonary aspergillosis. Am J Clin Pathol. 1986;86(4):518-23.

48. Marty FM, Koo S**.** Role of (1-->3)-beta-D-glucan in the diagnosis of invasive aspergillosis. Med Mycol. 2009;47 Suppl 1:S233-40.

49. Pfeiffer CD, Fine JP, Safdar N**.** Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis. 2006;42(10):1417-27.

50. Ostrosky-Zeichner L, Alexander BD, Kett DH, Vazquez J, Pappas PG, Saeki F, et al. Multicenter clinical evaluation of the (1-->3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis. 2005;41(5):654-9.

51. Marr KA, Laverdiere M, Gugel A, Leisenring W**.** Antifungal therapy decreases sensitivity of the Aspergillus galactomannan enzyme immunoassay. Clin Infect Dis. 2005;40(12):1762-9.

52. Odabasi Z, Mattiuzzi G, Estey E, Kantarjian H, Saeki F, Ridge RJ, et al. beta-D-glucan as a diagnostic adjunct for invasive fungal infections: Validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clinical Infectious Diseases. 2004;39(2):199-205.

53. Musher B, Fredricks D, Leisenring W, Balajee SA, Smith C, Marr KA**.** Aspergillus galactomannan enzyme immunoassay and quantitative PCR for diagnosis of invasive aspergillosis with bronchoalveolar lavage fluid. J Clin Microbiol. 2004;42(12):5517-22.

54. Marr KA, Balajee SA, McLaughlin L, Tabouret M, Bentsen C, Walsh TJ**.** Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. J Infect Dis. 2004;190(3):641-9.

55. Girmenia C, Perrone S**.** The diagnostic role of galactomannan during antifungal prophylaxis. Comment on: "The role of antifungal treatment in hematology". Haematologica 2012;97(3):325-7. Haematologica. 2012;97(10):e41.

56. Fisher BT, Zaoutis TE, Park JR, Bleakley M, Englund JA, Kane C, et al. Galactomannan Antigen Testing for Diagnosis of Invasive Aspergillosis in Pediatric Hematology Patients. J Pediatric Infect Dis Soc. 2012;1(2):103-11.

57. Maertens J, Verhaegen J, Demuynck H, Brock P, Verhoef G, Vandenberghe P, et al. Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive Aspergillosis. J Clin Microbiol. 1999;37(10):3223-8.

58. Viscoli C, Machetti M, Cappellano P, Bucci B, Bruzzi P, Van Lint MT, et al. False-positive galactomannan platelia Aspergillus test results for patients receiving piperacillin-tazobactam. Clin Infect Dis. 2004;38(6):913-6.

59. Maertens J, Theunissen K, Deeren D, Meersseman W, Van Eldere J**.** Defining a case of invasive aspergillosis by serum galactomannan. Medical Mycology. 2006;44:S173-S8.

60. Maertens J, Glasmacher A, Selleslag D, Ngai A, Ryan D, Layton M, et al. Evaluation of serum sandwich enzyme-linked immunosorbent assay for circulating galactomannan during caspofungin therapy: Results from the caspofungin invasive aspergillosis study. Clinical Infectious Diseases. 2005;41(1):E9-E14.

61. Maertens J, Theunissen K, Verhoef G, Van Eldere J**.** False-positive Aspergillus galactomannan antigen test results. Clinical Infectious Diseases. 2004;39(2):289-90.

62. Maertens JA, Theunissen K, Verschakelen J, Verhaegen J, Katrien L, Verbeken E, et al. Towards a lower cutoff for galactomannan detection in adult patients with hematological disorders. Blood. 2003;102(11):975a-a.

63. Maertens J, Van Eldere J, Verhaegen J, Verbeken E, Verschakelen J, Boogaerts M. Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. Journal of Infectious Diseases. 2002;186(9):1297-306.
64. Lamoth F. Galactomannan and 1,3-beta-d-Glucan Testing for the Diagnosis of Invasive Aspergillosis. J Fungi (Basel). 2016;2(3).
65. Maertens J, Theunissen K, Verhoef G, Verschakelen J, Lagrou K, Verbeken E, et al. Galactomannan and computed tomography - Based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: A prospective feasibility study. Clinical Infectious Diseases. 2005;41(9):1242-50.
66. Maertens J, Theunissen K, Verbeken E, Lagrou K, Verhaegen J, Boogaerts M, et al. Prospective clinical evaluation of lower cut-offs for galactomannan detection in adult neutropenic cancer patients and haematological stem cell transplant recipients. British Journal of Haematology. 2004;126(6):852-60.
67. Odabasi Z, Mattiuzzi G, Estey E, Kantarjian H, Saeki F, Ridge RJ, et al. Beta-D-glucan as a diagnostic adjunct for invasive fungal infections: validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clin Infect Dis. 2004;39(2):199-205.
68. Obayashi T, Negishi K, Suzuki T, Funata N. Reappraisal of the serum (1-->3)-beta-D-glucan assay for the diagnosis of invasive fungal infections--a study based on autopsy cases from 6 years. Clin Infect Dis. 2008;46(12):1864-70.
69. Yoshida M, Obayashi T, Iwama A, Ito M, Tsunoda S, Suzuki T, et al. Detection of plasma (1 --> 3)-beta-D-glucan in patients with Fusarium, Trichosporon, Saccharomyces and Acremonium fungaemias. J Med Vet Mycol. 1997;35(5):371-4.
70. Lamoth F, Akan H, Andes D, Cruciani M, Marchetti O, Ostrosky-Zeichner L, et al. Assessment of the Role of 1,3-beta-d-Glucan Testing for the Diagnosis of Invasive Fungal Infections in Adults. Clin Infect Dis. 2021;72(Supplement_2):S102-S8.
71. Lamoth F, Cruciani M, Mengoli C, Castagnola E, Lortholary O, Richardson M, et al. beta-Glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the Third European Conference on Infections in Leukemia (ECIL-3). Clin Infect Dis. 2012;54(5):633-43.
72. Shannon VR, Andersson BS, Lei X, Champlin RE, Kontoyiannis DP. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. Bone Marrow Transplant. 2010;45(4):647-55.
73. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization

for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2019.

74. Cornely OA, Maertens J, Bresnik M, Ebrahimi R, Ullmann AJ, Bouza E, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis. 2007;44(10):1289-97.

75. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347(6):408-15.

76. Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Ame S, Fohrer C, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis. 2008;47(9):1176-84.

77. Maertens JA, Raad, II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387(10020):760-9.

78. Maertens JA, Rahav G, Lee DG, Ponce-de-Leon A, Ramirez Sanchez IC, Klimko N, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet. 2021;397(10273):499-509.

79. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24 Suppl 1:e1-e38.

80. Patterson TF, Thompson GR, 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1-e60.

81. Neofytos D, Avdic E, Magiorakos AP**.** Clinical safety and tolerability issues in use of triazole derivatives in management of fungal infections. Drug Healthc Patient Saf. 2010;2:27-38.

82. Amigues I, Cohen N, Chung D, Seo SK, Plescia C, Jakubowski A, et al. Hepatic safety of voriconazole after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2010;16(1):46-52.

83. Wang TF, Wang T, Altman R, Eshaghian P, Lynch JP, 3rd, Ross DJ, et al. Periostitis secondary to prolonged voriconazole therapy in lung transplant recipients. Am J Transplant. 2009;9(12):2845-50.

84. Zonios DI, Gea-Banacloche J, Childs R, Bennett JE**.** Hallucinations during voriconazole therapy. Clin Infect Dis. 2008;47(1):e7-e10.

85. Imhof A, Schaer DJ, Schanz U, Schwarz U**.** Neurological adverse events to voriconazole: evidence for therapeutic drug monitoring. Swiss Med Wkly. 2006;136(45-46):739-42.

86. Dodds Ashley ES**.** Treatment options for invasive fungal infections. Pharmacotherapy. 2006;26(6 Pt 2):55S-60S.

87. den Hollander JG, van Arkel C, Rijnders BJ, Lugtenburg PJ, de Marie S, Levin MD**.** Incidence of voriconazole hepatotoxicity during intravenous and oral treatment for invasive fungal infections. J Antimicrob Chemother. 2006;57(6):1248-50.

88. Hoy Z, Dodds Ashley ES, Weinberg GA, Krysan DJ**.** Voriconazole Therapeutic Drug Monitoring. J Pediatric Infect Dis Soc. 2014;3(3):270-1.

89. Kim SH, Yim DS, Choi SM, Kwon JC, Han S, Lee DG, et al. Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients. Int J Infect Dis. 2011;15(11):e753-8.

90. Kim SH, Kwon JC, Park C, Han S, Yim DS, Choi JK, et al. Therapeutic drug monitoring and safety of intravenous voriconazole formulated with sulfobutylether beta-cyclodextrin in haematological patients with renal impairment. Mycoses. 2016;59(10):644-51.

91. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ**.** Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother. 2012;56(9):4793-9.

92. Park WB, Kim NH, Kim KH, Lee SH, Nam WS, Yoon SH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis. 2012;55(8):1080-7.

93. Neofytos D, Ostrander D, Shoham S, Laverdiere M, Hiemenz J, Nguyen H, et al. Voriconazole therapeutic drug monitoring: results of a prematurely discontinued randomized multicenter trial. Transpl Infect Dis. 2015;17(6):831-7.

94. Theuretzbacher U, Ihle F, Derendorf H**.** Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet. 2006;45(7):649-63.

95. Ceberio I, Dai K, Devlin SM, Barker JN, Castro-Malaspina H, Goldberg JD, et al. Safety of voriconazole and sirolimus coadministration after allogeneic hematopoietic SCT. Bone Marrow Transplant. 2015;50(3):438-43.

96. Zonios D, Yamazaki H, Murayama N, Natarajan V, Palmore T, Childs R, et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. J Infect Dis. 2014;209(12):1941-8.

97. Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol. 2009;65(3):281-5.

98. Scholz I, Oberwittler H, Riedel KD, Burhenne J, Weiss J, Haefeli WE, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. Br J Clin Pharmacol. 2009;68(6):906-15.

99. Weiss J, Ten Hoevel MM, Burhenne J, Walter-Sack I, Hoffmann MM, Rengelshausen J, et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J Clin Pharmacol. 2009;49(2):196-204.

100. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O**.** Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis. 2008;46(2):201-11.

101. Marr KA, Schlamm HT, Herbrecht R, Rottinghaus ST, Bow EJ, Cornely OA, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. Ann Intern Med. 2015;162(2):81-9.

102. Luke DR, Tomaszewski K, Damle B, Schlamm HT**.** Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). J Pharm Sci. 2010;99(8):3291-301.

103. Neofytos D, Lombardi LR, Shields RK, Ostrander D, Warren L, Nguyen MH, et al. Administration of voriconazole in patients with renal dysfunction. Clin Infect Dis. 2012;54(7):913-21.

104. Chan SY, Hughes RM, Woo K, Perales MA, Neofytos D, Papanicolaou G**.** Reasons for voriconazole prophylaxis discontinuation in allogeneic hematopoietic cell transplant recipients: A real-life paradigm. Med Mycol. 2020.

105. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, 3rd, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16(7):828-37.

106. Miceli MH, Kauffman CA**.** Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent. Clin Infect Dis. 2015;61(10):1558-65.

107. McCreary EK, Nguyen MH, Davis MR, Borlagdan J, Shields RK, Anderson AD, et al. Achievement of clinical isavuconazole blood concentrations in transplant recipients with isavuconazonium sulphate capsules administered via enteral feeding tube. J Antimicrob Chemother. 2020;75(10):3023-8.

108. Andes DR, Ghannoum MA, Mukherjee PK, Kovanda LL, Lu Q, Jones ME, et al. Outcomes by MIC Values for Patients Treated with Isavuconazole or Voriconazole for Invasive Aspergillosis in the Phase 3 SECURE and VITAL Trials. Antimicrob Agents Chemother. 2019;63(1).

109. Andes D, Kovanda L, Desai A, Kitt T, Zhao M, Walsh TJ**.** Isavuconazole Concentration in Real-World Practice: Consistency with Results from Clinical Trials. Antimicrob Agents Chemother. 2018;62(7).

110. Desai AV, Kovanda LL, Hope WW, Andes D, Mouton JW, Kowalski DL, et al. Exposure-Response Relationships for Isavuconazole in Patients with Invasive Aspergillosis and Other Filamentous Fungi. Antimicrob Agents Chemother. 2017;61(12).
111. Keirns J, Desai A, Kowalski D, Lademacher C, Mujais S, Parker B, et al. QT Interval Shortening With Isavuconazole: In Vitro and In Vivo Effects on Cardiac Repolarization. Clin Pharmacol Ther. 2017;101(6):782-90.
112. Rausch CR, DiPippo AJ, Bose P, Kontoyiannis DP**.** Breakthrough Fungal Infections in Patients With Leukemia Receiving Isavuconazole. Clin Infect Dis. 2018;67(10):1610-3.
113. DiPippo AJ, Rausch CR, Kontoyiannis DP**.** Tolerability of isavuconazole after posaconazole toxicity in leukaemia patients. Mycoses. 2019;62(1):81-6.
114. Hassouna H, Athans V, Brizendine KD**.** Real-world use-Isavuconazole at a large academic medical center. Mycoses. 2019;62(6):534-41.
115. Bose P, McCue D, Wurster S, Wiederhold NP, Konopleva M, Kadia TM, et al. Isavuconazole as Primary Anti-Fungal Prophylaxis in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome: An Open-Label, Prospective, Phase II Study. Clin Infect Dis. 2020.
116. Fontana L, Perlin DS, Zhao Y, Noble BN, Lewis JS, Strasfeld L, et al. Isavuconazole Prophylaxis in Patients With Hematologic Malignancies and Hematopoietic Cell Transplant Recipients. Clin Infect Dis. 2020;70(5):723-30.
117. Schwartz S, Cornely OA, Hamed K, Marty FM, Maertens J, Rahav G, et al. Isavuconazole for the treatment of patients with invasive fungal diseases involving the central nervous system. Med Mycol. 2020;58(4):417-24.
118. Kauffman CA, Malani AN, Easley C, Kirkpatrick P**.** Posaconazole. Nat Rev Drug Discov. 2007;6(3):183-4.
119. Dodds Ashley ES, Alexander BD**.** Posaconazole. Drugs Today (Barc). 2005;41(6):393-400.
120. Kontoyiannis DP, Lewis RE**.** Posaconazole prophylaxis in hematologic cancer. N Engl J Med. 2007;356(21):2214-5; author reply 5-8.
121. Krause DS**.** Posaconazole prophylaxis in hematologic cancer. N Engl J Med. 2007;356(21):2215; author reply -8.
122. Kwon DS, Mylonakis E**.** Posaconazole: a new broad-spectrum antifungal agent. Expert Opin Pharmacother. 2007;8(8):1167-78.
123. Schiller DS, Fung HB**.** Posaconazole: an extended-spectrum triazole antifungal agent. Clin Ther. 2007;29(9):1862-86.
124. Cornely OA, Duarte RF, Haider S, Chandrasekar P, Helfgott D, Jimenez JL, et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. J Antimicrob Chemother. 2016;71(6):1747.

125. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348-59.

126. De Pauw BE, Donnelly JP**.** Prophylaxis and aspergillosis--has the principle been proven? N Engl J Med. 2007;356(4):409-11.

127. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med. 2007;356(4):335-47.

128. Kuriakose K, Nesbitt WJ, Greene M, Harris B**.** Posaconazole-Induced Pseudohyperaldosteronism. Antimicrob Agents Chemother. 2018;62(5).

129. Thompson GR, 3rd, Beck KR, Patt M, Kratschmar DV, Odermatt A**.** Posaconazole-Induced Hypertension Due to Inhibition of 11beta-Hydroxylase and 11beta-Hydroxysteroid Dehydrogenase 2. J Endocr Soc. 2019;3(7):1361-6.

130. Davis MR, Nguyen MH, Gintjee TJ, Odermatt A, Young BY, Thompson GR**.** Management of posaconazole-induced pseudohyperaldosteronism. J Antimicrob Chemother. 2020;75(12):3688-93.

131. Nguyen MH, Davis MR, Wittenberg R, McHardy I, Baddley JW, Young BY, et al. Posaconazole Serum Drug Levels Associated With Pseudohyperaldosteronism. Clin Infect Dis. 2020;70(12):2593-8.

132. Marr KA, Seidel K, Slavin MA, Bowden RA, Schoch HG, Flowers ME, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood. 2000;96(6):2055-61.

133. Update E-C 2017;Pageshttp://www.ecil-leukaemia.com/telechargements/ECIL%207%20CMV%20final%20slides.pdf on September 30 2018.

134. Greer ND**.** Posaconazole (Noxafil): a new triazole antifungal agent. Proc (Bayl Univ Med Cent). 2007;20(2):188-96.

135. Jenks JD, Gangneux JP, Schwartz IS, Alastruey-Izquierdo A, Lagrou K, Thompson Iii GR, et al. Diagnosis of Breakthrough Fungal Infections in the Clinical Mycology Laboratory: An ECMM Consensus Statement. J Fungi (Basel). 2020;6(4).

136. Jenks JD, Cornely OA, Chen SC, Thompson GR, 3rd, Hoenigl M**.** Breakthrough invasive fungal infections: Who is at risk? Mycoses. 2020;63(10):1021-32.

137. Wasylyshyn A, Linder KA, Castillo CG, Zhou S, Kauffman CA, Miceli MH**.** Breakthrough Invasive Fungal Infections in Patients with Acute Myeloid Leukemia. Mycopathologia. 2020;185(2):299-306.

138. Fung M, Schwartz BS, Doernberg SB, Langelier C, Lo M, Graff L, et al. Breakthrough Invasive Fungal Infections on Isavuconazole Prophylaxis and Treatment: What Is Happening in the Real-World Setting? Clin Infect Dis. 2018;67(7):1142-3.

139. Morris SK, Allen UD, Gupta S, Richardson SE**.** Breakthrough filamentous fungal infections in pediatric hematopoetic stem cell transplant and oncology patients receiving caspofungin. Can J Infect Dis Med Microbiol. 2012;23(4):179-82.

140. Trifilio S, Singhal S, Williams S, Frankfurt O, Gordon L, Evens A, et al. Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. Bone Marrow Transplant. 2007;40(5):451-6.

141. Lionakis MS, Lewis RE, Kontoyiannis DP**.** Breakthrough Invasive Mold Infections in the Hematology Patient: Current Concepts and Future Directions. Clin Infect Dis. 2018;67(10):1621-30.

142. Cornely OA, Hoenigl M, Lass-Florl C, Chen SC, Kontoyiannis DP, Morrissey CO, et al. Defining breakthrough invasive fungal infection-Position paper of the mycoses study group education and research consortium and the European Confederation of Medical Mycology. Mycoses. 2019;62(9):716-29.

143. Stemler J, Koehler P, Maurer C, Muller C, Cornely OA**.** Antifungal prophylaxis and novel drugs in acute myeloid leukemia: the midostaurin and posaconazole dilemma. Ann Hematol. 2020;99(7):1429-40.

144. Agarwal SK, DiNardo CD, Potluri J, Dunbar M, Kantarjian HM, Humerickhouse RA, et al. Management of Venetoclax-Posaconazole Interaction in Acute Myeloid Leukemia Patients: Evaluation of Dose Adjustments. Clin Ther. 2017;39(2):359-67.

145. Cornely OA, Ullmann AJ**.** Numbers needed to treat with posaconazole prophylaxis to prevent invasive fungal infection and death. Clin Infect Dis. 2008;46(10):1626-7; author reply 7-8.

146. Kraljevic M, Khanna N, Medinger M, Passweg J, Masouridi-Levrat S, Chalandon Y, et al. Clinical considerations on posaconazole administration and therapeutic drug monitoring in allogeneic hematopoietic cell transplant recipients. Med Mycol. 2020.

147. Horn DL, Fishman JA, Steinbach WJ, Anaissie EJ, Marr KA, Olyaei AJ, et al. Presentation of the PATH Alliance registry for prospective data collection and analysis of the epidemiology, therapy, and outcomes of invasive fungal infections. Diagn Microbiol Infect Dis. 2007;59(4):407-14.

148. Steinbach WJ, Marr KA, Anaissie EJ, Azie N, Quan SP, Meier-Kriesche HU, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect. 2012;65(5):453-64.

149. Pfaller MA, Andes DR, Diekema DJ, Horn DL, Reboli AC, Rotstein C, et al. Epidemiology and outcomes of invasive candidiasis due to non-albicans species of Candida in 2,496 patients: data from the Prospective Antifungal Therapy (PATH) registry 2004-2008. PLoS One. 2014;9(7):e101510.

150. Neofytos D, Huprikar S, Reboli A, Schuster M, Azie N, Franks B, et al. Treatment and outcomes of Candida osteomyelitis: review of 53 cases from the PATH Alliance(R) registry. Eur J Clin Microbiol Infect Dis. 2014;33(1):135-41.

151. Kontoyiannis DP, Azie N, Franks B, Horn DL**.** Prospective antifungal therapy (PATH) alliance((R)) : focus on mucormycosis. Mycoses. 2014;57(4):240-6.

152. Husain S, Silveira FP, Azie N, Franks B, Horn D**.** Epidemiological features of invasive mold infections among solid organ transplant recipients: PATH Alliance(R) registry analysis. Med Mycol. 2017;55(3):269-77.

153. Burkhardt O, Thon S, Burhenne J, Welte T, Kielstein JT**.** Sulphobutylether-beta-cyclodextrin accumulation in critically ill patients with acute kidney injury treated with intravenous voriconazole under extended daily dialysis. International Journal of Antimicrobial Agents. 2010;36(1):93-4.

154. Hafner V, Czock D, Burhenne J, Riedel KD, Bommer J, Mikus G, et al. Pharmacokinetics of Sulfobutylether-Beta-Cyclodextrin and Voriconazole in Patients with End-Stage Renal Failure during Treatment with Two Hemodialysis Systems and Hemodiafiltration. Antimicrobial Agents and Chemotherapy. 2010;54(6):2596-602.

155. Hafner V, Czock D, Burhenne J, Riedel KD, Bommer J, Mikus G, et al. Pharmacokinetics of the Solvent Sulfobutylether-Beta-Cyclodextrin (Sbecd) in Patients with Chronic Renal Failure during Haemodialysis Treatment with Two Systems and Haemodiafiltration. British Journal of Clinical Pharmacology. 2009;68:20-.

156. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative w**.** Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204-12.

157. Jang SH, Colangelo PM, Gobburu JVS**.** Exposure-Response of Posaconazole Used for Prophylaxis Against Invasive Fungal Infections: Evaluating the Need to Adjust Doses Based on Drug Concentrations in Plasma. Clinical Pharmacology & Therapeutics. 2010;88(1):115-9.

158. Rauseo AM, Coler-Reilly A, Larson L, Spec A**.** Hope on the Horizon: Novel Fungal Treatments in Development. Open Forum Infect Dis. 2020;7(2):ofaa016.

159. Gintjee TJ, Donnelley MA, Thompson GR, 3rd**.** Aspiring Antifungals: Review of Current Antifungal Pipeline Developments. J Fungi (Basel). 2020;6(1).

160. Wring SA, Randolph R, Park S, Abruzzo G, Chen Q, Flattery A, et al. Preclinical Pharmacokinetics and Pharmacodynamic Target of SCY-078, a First-in-Class Orally Active Antifungal Glucan Synthesis Inhibitor, in Murine Models of Disseminated Candidiasis. Antimicrob Agents Chemother. 2017;61(4).

161. Pfaller MA, Messer SA, Rhomberg PR, Borroto-Esoda K, Castanheira M**.** Differential Activity of the Oral Glucan Synthase Inhibitor SCY-078 against Wild-Type and Echinocandin-Resistant Strains of Candida Species. Antimicrob Agents Chemother. 2017;61(8).

162. Lee A, Prideaux B, Zimmerman M, Carter C, Barat S, Angulo D, et al. Penetration of Ibrexafungerp (Formerly SCY-078) at the Site of Infection in an Intra-abdominal Candidiasis Mouse Model. Antimicrob Agents Chemother. 2020;64(3).

163. Wring S, Murphy G, Atiee G, Corr C, Hyman M, Willett M, et al. Lack of Impact by SCY-078, a First-in-Class Oral Fungicidal Glucan Synthase Inhibitor, on the Pharmacokinetics of Rosiglitazone, a Substrate for CYP450 2C8, Supports the Low Risk for Clinically Relevant Metabolic Drug-Drug Interactions. J Clin Pharmacol. 2018;58(10):1305-13.

164. Wring S, Murphy G, Atiee G, Corr C, Hyman M, Willett M, et al. Clinical Pharmacokinetics and Drug-Drug Interaction Potential for Coadministered SCY-078, an Oral Fungicidal Glucan Synthase Inhibitor, and Tacrolimus. Clin Pharmacol Drug Dev. 2019;8(1):60-9.

165. Oliver JD, Sibley GEM, Beckmann N, Dobb KS, Slater MJ, McEntee L, et al. F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(45):12809-14.

166. Beckmann N, DuPre S, Law D, Read N, Sibley G, Oliver J, et al. Introducing the orotomide F901318: a potent antifungal agent acting through a novel mechanism of action. Mycoses. 2016;59:36-.

167. Kirchhoff L, Dittmer S, Buer J, Rath PM, Steinmann J**.** In vitro activity of olorofim (F901318) against fungi of the genus, Scedosporium and Rasamsonia as well as against Lomentospora prolificans, Exophiala dermatitidis and azole-resistant Aspergillus fumigatus. International Journal of Antimicrobial Agents. 2020;56(3).

168. du Pre S, Birch M, Law D, Beckmann N, Sibley GEM, Bromley MJ, et al. The Dynamic Influence of Olorofim (F901318) on the Cell Morphology and Organization of Living Cells ofAspergillus fumigatus. Journal of Fungi. 2020;6(2).

169. du Pre S, Beckmann N, Almeida MC, Sibley GEM, Law D, Brand AC, et al. Effect of the Novel Antifungal Drug F901318 (Olorofim) on Growth and Viability of Aspergillus fumigatus. Antimicrobial Agents and Chemotherapy. 2018;62(8).

170. Miyazaki M, Horii T, Hata K, Watanabe N, Nakamoto K, Tanaka K, et al. In Vitro Activity of E1210, a Novel Antifungal, against Clinically Important Yeasts and Molds. Antimicrobial Agents and Chemotherapy. 2011;55(10):4652-8.

171. Pfaller MA, Watanabe N, Castanheira M, Messer SA, Jones RN**.** Pre-clinical development of antifungal susceptibility test methods for the testing of the novel antifungal agent E1210 versus Candida: comparison of CLSI and European Committee on Antimicrobial Susceptibility Testing methods. Journal of Antimicrobial Chemotherapy. 2011;66(11):2581-4.

172. Nakamura I, Ohsumi K, Takeda S, Katsumata K, Matsumoto S, Akamatsu S, et al. ASP2397 Is a Novel Natural Compound That Exhibits Rapid and Potent Fungicidal Activity against Aspergillus Species through a Specific Transporter. Antimicrob Agents Chemother. 2019;63(10).

173. Nakamura I, Yoshimura S, Masaki T, Takase S, Ohsumi K, Hashimoto M, et al. ASP2397: a novel antifungal agent produced by Acremonium persicinum MF-347833. J Antibiot (Tokyo). 2017;70(1):45-51.

174. Nakamura I, Kanasaki R, Yoshikawa K, Furukawa S, Fujie A, Hamamoto H, et al. Discovery of a new antifungal agent ASP2397 using a silkworm model of Aspergillus fumigatus infection. J Antibiot (Tokyo). 2017;70(1):41-4.

175. Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med. 2009;361(18):1760-7.

176. Plantinga TS, van der Velden WJFM, Ferwerda B, van Spriel AB, Adema G, Feuth T, et al. Early Stop Polymorphism in Human DECTIN-1 Is Associated with Increased Candida Colonization in Hematopoietic Stem Cell Transplant Recipients. Clinical Infectious Diseases. 2009;49(5):724-32.

177. Sainz J, Lupianez CB, Segura-Catena J, Vazquez L, Rios R, Oyonarte S, et al. Dectin-1 and DC-SIGN Polymorphisms Associated with Invasive Pulmonary Aspergillosis Infection. Plos One. 2012;7(2).

178. Salvatori G, Campo S**.** Current understanding of PTX3 protective activity on Aspergillus fumigatus infection. Medical Mycology. 2012;50(3):225-33.

179. Fischer M, Spies-Weisshart B, Schrenk K, Gruhn B, Wittig S, Glaser A, et al. Polymorphisms of Dectin-1 and TLR2 Predispose to Invasive Fungal Disease in Patients with Acute Myeloid Leukemia. Plos One. 2016;11(3).

APPENDIX 1-5

MAJOR ARTICLE

Epidemiology and Outcome of Invasive Fungal Infection in Adult Hematopoietic Stem Cell Transplant Recipients: Analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance Registry

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Background. With use of data from the Prospective Antifungal Therapy (PATH) Alliance registry, we performed this multicenter, prospective, observational study to assess the epidemiologic characters and outcomes of invasive fungal infection (IFI) in hematopoietic stem cell transplant (HSCT) recipients.

Methods. Sixteen medical centers from North America reported data on adult HSCT recipients with proven or probable IFI during the period July 2004 through September 2007. The distribution of IFIs and rates of survival at 6 and 12 weeks after diagnosis were studied. We used logistic regression models to determine risk factors associated with 6-week mortality for allogeneic HSCT recipients with invasive aspergillosis (IA).

Results. Two hundred thirty-four adult HSCT recipients with a total of 250 IFIs were included in this study. IA (59.2%) was the most frequent IFI, followed by invasive candidiasis (24.8%), zygomycosis (7.2%), and IFI due to other molds (6.8%). Voriconazole was the most frequently administered agent (68.4%); amphotericin B deoxycholate was administered to a few patients (2.1%). Ninety-three (46.7%) of 199 HSCT recipients with known outcome had died by week 12. The 6-week survival rate was significantly greater for patients with IA than for those with invasive candidiasis and for those with IFI due to the Zygomycetes or other molds ($P < .001$). The 6-week mortality rate for HSCT recipients with IA was 21.5%. At 6 weeks, there was a trend toward a worse outcome among allogeneic HSCT recipients with IA who received myeloablative conditioning ($P = .07$); absence of mechanical ventilation or/and hemodialysis ($P = .01$) were associated with improved survival.

Conclusions. IA remains the most commonly identified IFI among HSCT recipients, but rates of survival in persons with IA appear to have improved, compared with previously reported data. Invasive candidiasis and IFI due to molds other than *Aspergillus* species remain a significant problem in HSCT recipients.

Hematopoietic stem cell transplant (HSCT) recipients have a high risk of acquiring invasive fungal infection (IFI) by virtue of cytopenias and receipt of therapies to prevent and treat graft-versus-host disease. During the past 2 decades, the epidemiology of IFI has changed: fluconazole prophylaxis has been successfully used to prevent *Candida albicans* infection [1, 2], and mold infections have become more common [3, 4]. Changes in transplantation practices, including the sources used for stem cells, conditioning regimens, and strategies to diagnose and treat IFI, have likely impacted the epi-

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demiology and outcomes of IFI. However, most recent data are limited to single-center studies [3–6].

The Prospective Antifungal Therapy (PATH) Alliance is a prospective, multicenter, observational registry that collects data and monitors trends in the epidemiologic characteristics, diagnosis, treatment, and outcomes of IFI in North America. We performed this multicenter, prospective, observational study to assess the epidemiology and outcomes of IFI in HSCT recipients.

METHODS

Case identification and data collection. The PATH Alliance consists of 23 medical centers in the United States and Canada. Data are entered prospectively into electronic case report forms with use of methods that have been described elsewhere [7]. This study was performed by review of data registered by 16 medical centers that reported at least 1 adult (age, ⩾19 years) HSCT recipient with a proven or probable IFI during the period July 2004 through September 2007.

Variables collected included the subject's demographic characteristics, underlying disease, transplant characteristics, type of IFI, and outcome. Underlying disease and transplant characteristics included data on the type and state of hematologic malignancy or other underlying disease, gastrointestinal tract mucositis, conditioning regimen, stem cell manipulation, history of prior HSCT, stem cell source, and presence and severity of graft-versus-host disease (defined as acute [grade II–IV] or chronic). In addition, information on the following immunologic risk factors was collected: absolute neutrophil count, receipt of total body irradiation, donor lymphocyte infusion, use of corticosteroids (within 30 days before the diagnosis), and use of other immunosuppressive agents. The following host data were collected: demographic characteristics, receipt of prior antifungal therapy (within 30 days before the diagnosis of IFI), organ function, organ support requirements, and concomitant viral or bacterial infection (within 30 and 7 days before the diagnosis of IFI, respectively). Detailed information pertaining to the IFI was collected, including the time after HSCT, fungal genus and species (when isolated), diagnostic modalities, site of infection, antifungal therapy history, and therapeutic procedures.

Definitions. IFIs were defined in accordance with published guidelines [8]. The day of diagnosis was defined as the day that the first positive culture or pathologic test result was provided to the treating physician. The outcome of IFI therapy was recorded at final assessment (i.e., 12 weeks after diagnosis of IFI) as complete or partial response, stable condition, worsening condition, or unknown, as assessed by investigators and as described elsewhere [7].

Analyses. The distribution of IFIs across the different types of HSCTs and crude mortality rates at weeks 6 and 12 are described. Survival analyses were performed on the basis of the type of the HSCT (allogeneic transplant from an unrelated or unmatched, related donor; or autologous transplant), the different IFIs (invasive candidiasis [IC], invasive aspergillosis [IA], or IFI due to the Zygomycetes or other molds), and type of conditioning regimen (myeloablative vs. nonmyeloablative; for allogeneic HSCT recipients only).

We used logistic regression analysis to determine the major risk factors associated with 6-week mortality for allogeneic HSCT recipients with IA, excluding patients who received cord blood transplants. Risk factors evaluated for IA-associated mortality included the following variables: age, HSCT type (allogeneic transplant from an unrelated or unmatched, related donor), stem cell source (peripheral blood vs. bone marrow), conditioning regimen (myeloablative vs. nonmyeloablative), organ support (dialysis dependence or/and mechanical ventilation), cytomegalovirus infection, and disease risk ("high risk" was defined as acute or chronic lymphocytic leukemia, lymphoma, multiple myeloma, or acute myelogenic leukemia not in first remission; "low risk" was defined as all the rest of the hematologic malignancies). Different models were constructed on the basis of the interval between transplantation and diagnosis: one for early diagnosis of infection (⩽40 days after transplantation) and the other for late diagnosis of infection (>40 days after transplantation). Because of the small number of patients, risk factor analysis for mortality was not performed for patients with IC or with IFI due to molds other than *Aspergillus* species.

Comparisons between categorical variables were performed by Fisher's exact test or the χ^2 test; for continuous variables, Student's t test or analysis of variance was used. Survival distribution function was estimated using the Kaplan-Meier product-limit method. Bivariate analyses and cluster analysis were used to screen for potential mortality risk factors from a list of clinically significant variables; the final mortality risk factors were then determined through stepwise logistic regression with a .1 significant level.

RESULTS

Baseline patient characteristics. Two hundred thirty-four adult HSCT recipients with a total of 250 proven or probable IFIs were included in this study. A total of 161 patients (68.8%) had received an allogeneic HSCT, and 73 (31.2%) had received an autologous HSCT. Among the allogeneic HSCT recipients, 63 (39.1%) patients had received an HLA-matched HSCT from a related donor, 59 (36.6%) had received an HLA-matched HSCT from an unrelated donor, 31 (19.3%) had received an HLA-mismatched HSCT, and 8 (5.0%) had received a haploidentical HSCT. Sixteen medical centers contributed a median of 5.5 patients each (range, 2–93 patients). Of note, 147 HSCT

recipients (62.8%) with IFI were reported by 2 centers (93 and 54 patients) (figure 1).

Detailed descriptions of the patients' baseline characteristics, underlying disease, comorbidity, and HSCT specifics are presented in table 1. A significant number of autologous HSCT recipients were treated with corticosteroids (55 patients [75.3%]) and 2 patients (2.7%) in this group received other immunosuppressive agents. More than one-third (58 patients [36.0%]) of allogeneic HSCT recipients had acute (grade II–IV) or chronic graft-versus-host disease. Among the 161 allogeneic HSCT recipients, calcineurin inhibitors were the most commonly administered immunosuppressive agents (118 patients [73.3%]), followed by mycophenolate mofetil (53 patients [32.9%]), and sirolimus (9 patients [5.6%]).

IFI. The distribution of IFIs is outlined in table 2. IA was the most commonly observed IFI (148 [59.2%] of 250 cases), followed by IC (62 cases [24.8%]), zygomycosis (18 cases [7.2%]), and IFI due to other molds (17 cases [6.8%]). There were no notable differences in the distribution of IFIs across the different HSCT categories. The frequency of IFI, as reported by the participating centers of the PATH Alliance during 2004–2007, appeared to have changed over time. In contrast to cases of IA that remained relatively stable during 2005–2006, the frequency of IC has decreased, whereas that of IFI due to Zygomycetes and other molds appears to have increased (data not shown). *Aspergillus fumigatus* was the most frequently isolated *Aspergillus* species (55 [37.2%] of 148 cases), whereas the species were not identified in 78 cases (52.7%) of IA. The diagnosis of IA was proven in 17 cases (11.5%) and was considered probable in 131 cases (88.5%). The galactomannan assay (in the serum and/or bronchoalveolar lavage fluid specimens) was used for diagnosis of 108 cases (73.0%) of IA. The majority of cases of IC were due to non-*albicans* species of *Candida* (47 [75.8%] of 62 cases); *Candida glabrata* was the most frequently isolated species (27 [43.5%] of 62 cases), and 7 cases (11.3%) were due to *Candida krusei.*

The interval between HSCT and diagnosis of IFI was studied for patients with a single IFI (figure 2). The median time after HSCT was 77 days (range, 0–2219 days) for IC and 82 days (range, 3–6542 days) for IA. There was a trend for IC to occur earlier after transplantation in autologous HSCT recipients (median interval, 28 days; range, 6–1559 days) than in allogeneic HSCT recipients (median interval, 108 days; range, 0–2219 days; $P = .11$). In contrast, the interval between HSCT and IA diagnosis for autologous HSCT recipients (median, 51 days; range, 3–2065 days) and allogeneic HSCT recipients (median, 83 days; range, 3–6542 days) did not appear to differ significantly ($P = .63$). IFI due to Zygomycetes and other molds occurred late after HSCT (median interval, 173 days; range, 7–2254 days); it tended to occur later in autologous HSCT recipients (median interval, 412 days; range, 190–2254 days) than in allogeneic HSCT recipients (median interval, 162 days; range, 7–932 days; $P = .21$). When the interval between HSCT and IFI diagnosis was studied separately for the different allogeneic HSCT categories (matched, related donor vs. other), no major differences were observed (data not shown). Allogeneic HSCT recipients who received a myeloablative conditioning regimen were more likely to receive a diagnosis of IC early after HSCT (median interval, 65 days; range, 0–1594 days), compared with those who received a nonmyeloablative conditioning regimen (median interval, 590 days; range, 120–2219 days; $P = .26$). In contrast, no major differences in the interval between HSCT and diagnosis of IFI due to molds were observed between allogeneic HSCT recipients on the basis of their conditioning regimens (data not shown).

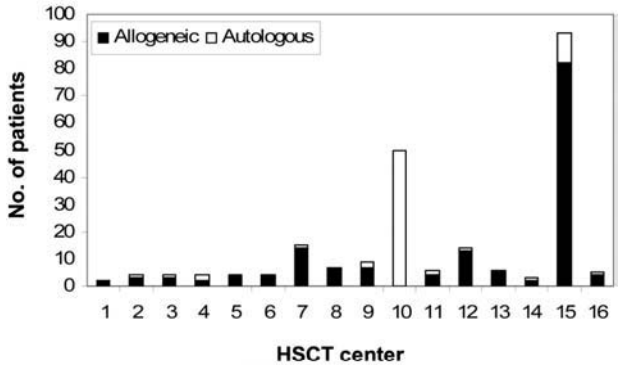

Figure 1. Number of patients contributed by the Prospective Antifungal Therapy (PATH) Alliance participating centers, presented on the basis of hematopoietic stem cell transplant (HSCT) category (allogeneic vs. autologous) across 16 transplantation centers.

Antifungal therapy. Overall, voriconazole was the most frequently administered agent (160 patients [68.4%]), followed by caspofungin (115 patients [49.1%]) and the lipid formulations of amphotericin B (99 patients [42.3%]). Of note, amphotericin B deoxycholate was administered to few patients (5 patients [2.1%]). For IC, caspofungin was the most frequently administered agent (30 [52.6%] of 57 patients), followed by the lipid formulations of amphotericin B (20 patients [35.1%]) and fluconazole (18 patients [31.6%]). The vast majority of patients with IA (122 [84.7%] of 144 patients) and with IFI due to other molds (13 [76.5%] of 17 patients) received therapy with voriconazole. The lipid formulations of amphotericin B were more frequently administered in cases of zygomycosis (15 [83.3%] of 18 cases) (figure 3). Combination therapy, defined as concomitant administration of $\geqslant 2$ antifungal agents, was most commonly used in cases of IA (68 [47.2%] of 144 patients), IFI due to other molds (9 patients [52.9%]), and zygomycosis (6 patients [33.3%]). Treatment with voriconazole plus the echinocandins was the most frequently used combination regimen for patients with IA (56 [82.4%] of 68 patients who received voriconazole combination therapy); voriconazole

Table 1. Baseline patient characteristics for 234 hematopoietic stem cell transplant (HSCT) recipients.

Variable	HSCT category		
	Allogeneic transplant		
	Matched, related donor (n = 63)	Unrelated or unmatched, related donor[a] (n = 98)	Autologous transplant (n = 73)
Demographic characteristic			
Age, years			
Mean ± SE	48.7 ± 1.73	50.62 ± 1.41	57.8 ± 1.3
Range	19.5–74.3	19.1–74.4	23.8–76.9
Male sex	38 (60.3)	59 (60.2)	41 (56.2)
White ethnicity	54 (85.7)	62 (63.3)	62 (84.9)
Underlying disease[b]			
Acute leukemia	36 (57.1)	47 (48.0)	1 (1.4)
Chronic leukemia	7 (11.1)	14 (14.3)	1 (1.4)
Lymphoma	10 (15.9)	21 (21.4)	19 (26.0)
Multiple myeloma	4 (6.3)	5 (5.1)	50 (68.5)
Myelodysplastic syndrome	8 (12.7)	16 (16.3)	1 (1.4)
Other[c]	3 (4.8)	3 (3.1)	4 (5.5)
Transplant characteristic			
Stem cell source			
Bone marrow	10 (15.9)	18 (18.4)	2 (2.7)
Peripheral blood	53 (84.1)	70 (71.4)[d]	70 (95.9)
Stem cell manipulation: T cell depletion	5 (7.9)	6 (6.1)	1 (1.4)
CD34 selected	6 (9.5)	6 (6.1)	3 (4.1)
Receipt of myeloablative conditioning	42 (66.7)	62 (63.3)	73 (100.0)
Prior HSCT	7 (11.1)	25 (25.5)	41 (56.2)
Organ function[b] and transplantation complications			
Dialysis dependence	2 (3.2)	7 (7.1)	10 (13.7)
Diabetes mellitus	26 (41.3)	48 (49.0)	16 (21.9)
Requirement of total parenteral nutrition	26 (41.3)	44 (44.9)	11 (15.1)
Mechanical ventilation	8 (12.7)	8 (8.2)	14 (19.2)
GVHD			
Acute (grade II–IV)	20 (31.7)	38 (38.8)	1 (1.4)
Chronic	15 (23.8)	18 (18.4)	0 (0)
Mucositis (grade I–IV)	11 (17.5)	21 (21.4)	23 (31.5)
Cytomegalovirus infection	5 (7.9)	15 (15.3)	8 (11.0)
Bacterial infection	25 (39.7)	38 (38.8)	28 (38.4)
Immunologic risk factors[b]			
Absolute neutrophil count, <500 cells/mm^3	28 (44.4)	57 (58.2)	51 (69.9)
Total body irradiation	8 (12.7)	26 (26.5)	4 (5.5)
Donor lymphocyte infusion	2 (3.2)	4 (4.1)	3 (4.1)
Receipt of corticosteroid therapy	49 (77.8)	69 (70.4)	55 (75.3)
Receipt of immunosuppressive therapy	45 (71.4)	87 (88.8)	2 (2.7)

NOTE. Data are no. (%) of patients, unless otherwise indicated. GVHD, graft-versus-host disease.

[a] Includes 59 recipients of HSCTs from HLA-matched, unrelated donors; 8 recipients of transplants from haploidentical donors; and 31 recipients of transplants from HLA-mismatched donors.

[b] Underlying disease, organ function, and immunologic risk factors were not mutually exclusive (i.e., patients could have >1 factor).

[c] One recipient of an HSCT from a matched, related donor and 2 recipients of autologous HSCTs had a solid tumor, and 2 recipients of allogeneic HSCTs from unrelated donors had a surgical condition. The remaining patients had another hematologic condition.

[d] The stem cell source for 10 recipients of allogeneic HSCTs from unrelated donors was cord blood.

Table 2. Distribution of infecting fungal pathogens and species observed in 234 hematopoietic stem cell transplant (HSCT) recipients with a total of 250 invasive fungal infections (IFIs).

IFI	HSCT category		
	Allogeneic transplant		
	Matched, related donor (n = 71)	Unrelated or unmatched, related donor[a] (n = 102)	Autologous transplant (n = 77)
Candida species			
All	20 (28.2)	23 (22.5)[b]	19 (24.7)
Candida albicans	5 (25.0)	4 (17.4)	6 (31.6)
Candida glabrata	7 (35.0)	13 (56.5)	7 (36.8)
Candida krusei	2 (10.0)	2 (8.7)	3 (15.8)
Candida parapsilosis	3 (30.0)	2 (8.7)	2 (10.5)
Candida tropicalis	3 (30.0)	1 (4.3)	1 (5.3)
Aspergillus species			
All	38 (53.5)	61 (59.8)	49 (63.6)
Aspergillus flavus	2 (5.3)	1 (1.6)	2 (4.1)
Aspergillus fumigatus	16 (42.1)	27 (44.3)	12 (24.5)
Aspergillus niger	2 (5.3)	2 (3.3)	1 (2.0)
Aspergillus terreus	1 (2.6)	0 (0)	0 (0)
Other	1 (2.6)	2 (3.3)	1 (2.0)
Unknown	16 (42.1)	29 (47.5)	33 (67.3)
Zygomycetes			
All	6 (8.5)	6 (5.9)	6 (7.8)
Absidia species	1 (16.7)	1 (16.7)	0 (0)
Mucor/Rhizomucor species	1 (16.7)	1 (16.7)	1 (16.7)
Rhizopus species	3 (50.0)	3 (50.0)	4 (66.6)
Other	1 (16.7)	1 (16.7)	1 (16.7)
Endemic fungi[c]	1 (1.4)	0 (0)	0 (0)
Other yeast[d]	0 (0)	4 (3.9)	0 (0)
Other molds			
All	6 (8.5)	8 (7.8)	3 (3.9)
Fusarium species	2 (33.3)	2 (25.0)	0 (0)

NOTE. IFIs were not mutually exclusive; patients could have >1 IFI. Two hundred nineteen patients had only 1 IFI. Fourteen patients had 2 concomitant IFIs: 3 had IFIs due to 2 different *Candida* species, 4 had IFIs due to *Candida* and *Aspergillus* species, 4 had IFIs due to 2 different *Aspergillus* species, and 3 had IFIs due to *Rhizopus* species plus *C. glabrata, A. fumigatus,* or an unknown *Aspergillus* species. One HSCT recipient had 3 concomitant IFIs due to 2 different *Candida* species and an unknown yeast.

[a] Included 59 recipients of HSCTs from HLA-matched, unrelated donors; 8 recipients of HSCTs from haploidentical donors; and 31 recipients of HSCTs from HLA-mismatched donors.

[b] One case of IFI due to *Candida guilliermondii* was observed.

[c] Endemic fungi included 1 case involving *Histoplasma* species.

[d] Other yeasts included *Saccharomyces* species (2 cases) and *Malassezia* and *Trichosporon* species (1 case each).

plus caspofungin was the most frequently used type of this particular combination regimen (47 patients [69.1%]).

Outcomes. A total of 35 of 234 HSCT recipients with IFI were lost to follow-up during the 12-week observation period. Of the remaining 199 patients, 93 (46.7%) died. Survival did not differ when patients were analyzed on the basis of HSCT type (allogeneic transplant from a matched, related donor vs. allogeneic transplant from other donor vs. autologous transplant; $P = .85$). For patients with only 1 IFI, after exclusion of patients who were lost to follow-up, IFI due to other molds was associated with the highest 12-week mortality rate (80.0% [12 of 15 patients]), followed by zygomycosis (64.3% [9 of 14

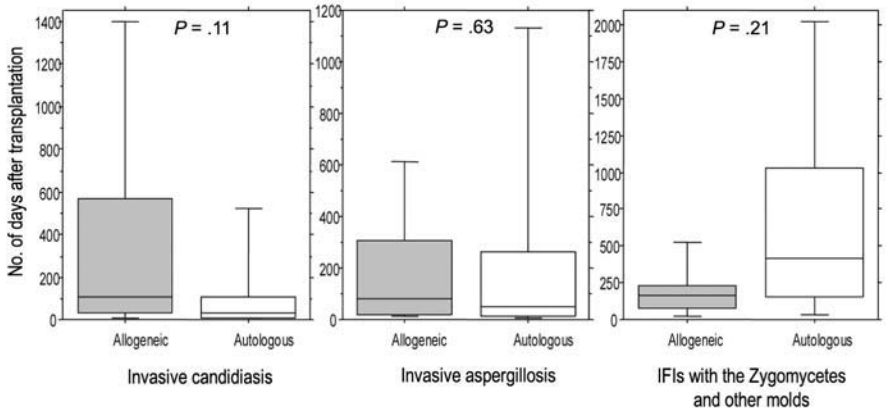

Figure 2. Interval between diagnosis of invasive fungal infection (IFI) after hematopoietic stem cell transplantation (HSCT; patients with only 1 infection were included) for allogeneic versus autologous HSCT recipients. *P* value is for a comparison of allogeneic and autologous HSCT groups.

patients]) and IC (48.9% [22 of 45 patients]). Patients with IA had the lowest 12-week mortality rate in this study (35.5% [38 of 107 patients]). The 6-week survival rate was significantly better for HSCT recipients with IA, followed by those with IC and those with IFI due to Zygomycetes or other molds, who had the highest mortality rate ($P < .001$) (figure 4*A*). Response to treatment was assessed by investigators at 12 weeks after the diagnosis of IFI (figure 4*B*). The majority of HSCT recipients with IC (42 [67.7%] of 62 patients) and with IA (94 [63.5%] of 148 patients) were reported to have responded (completely or partially) to the administered therapy. In contrast, 10 (55.6%) of 18 patients with zygomycosis and 6 (35.3%) of 17 with IFI due to other molds demonstrated a worsening of their clinical status at follow-up.

In 6-week survival analyses performed for HSCT recipients with IA only, there were no significant differences observed in the survival rate based on the certainty of diagnosis (proven vs. probable), the HSCT type (allogenic vs. autologous), or the interval between HSCT and diagnosis (≤40 days vs. >40 days; data not shown). However, there appeared to be a trend toward worse outcome at 6 weeks among allogeneic HSCT recipients with IA who received myeloablative conditioning ($P = .07$).

We performed bivariate analyses to assess risk factors for death at 6 weeks after the diagnosis of IA in allogeneic HSCT recipients; the variables examined are detailed in Methods. Nonmyeloablative conditioning ($P = .01$) and absence of mechanical ventilation or/and hemodialysis ($P = .01$) were associated with improved survival rates. Because the variables examined were associated with the interval between HSCT and diagnosis, we performed separate analyses based on the timing of the diagnosis of IA. For the early time period (i.e., ≤40 days after transplantation), data on 30 patients with IA were included in bivariate and multivariate analyses. The bivariate 6-week exploratory analyses revealed trends toward improved survival associated with a lack of severe organ failure (as evidenced by dialysis and mechanical ventilation; $P = .08$) and receipt of a nonmyeloablative conditioning regimen ($P = .07$). When these variables were introduced in a multivariate model, only severe organ dysfunction (OR, 1.60; $P = .10$) continued to demonstrate a trend toward higher mortality risk. Similarly, in bivariate analyses for late diagnoses (i.e., >40 days after transplantation), survival rates seemed to be better for patients who had received a nonmyeloablative condition regimen ($P = .12$) and who did not require dialysis or/and mechanical ventilation ($P = .02$).

DISCUSSION

We performed this multicenter, prospective, observational study to evaluate the contemporary epidemiologic characteristics, clinical presentations, and outcomes of IFI in 234 adult HSCT recipients during the period 2004–2007. Important findings include persistently high rates of IA, with possible improvements in IA-associated mortality, and poor outcomes associated with other fungal infection after HSCT.

Mortality rates for HSCT recipients with IA have historically been as high as 80%, although most studies were performed before the extensive use of voriconazole for the treatment of IA [3, 9, 10]. However, recent data suggest that outcomes appear to be improving [11]. We report 6- and 12-week mortality rates of 21.5% and 35.5%, respectively, among HSCT recipients with IA, which is markedly improved over rates from prior reports of outcomes during the 1990s. The observed 12-week survival rate is consistent with that reported by Herbrecht et al. [12] in the original validation trial of voriconazole for the treatment of IA, although only a minority of patients in that study had undergone HSCT. An analysis of that study suggested that assessment of clinical outcome and mortality at 6 weeks after diagnosis may be more reflective of IA-associated mortality [13]; the 21.5% estimated mortality rate in our data set

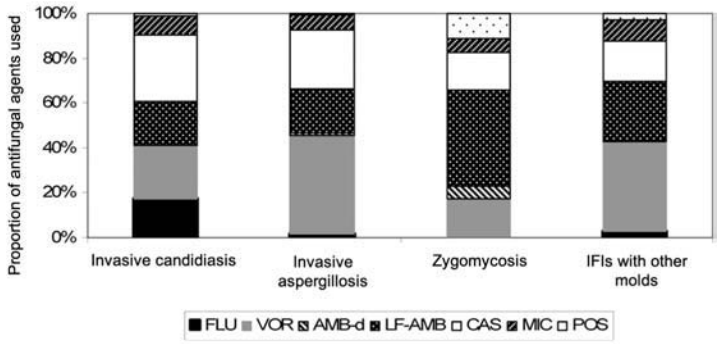

Figure 3. Distribution of antifungal agents based on the most commonly observed invasive fungal infections (IFIs). Four patients with invasive aspergillosis received therapy with fluconazole (FLU), all in combination with other agents. Four patients with zygomycosis were treated with voriconazole (VOR); 3 of them received combination therapy with other agents, and 1 was treated with VOR alone; all patients died. One patient with an IFI due to other molds received treatment with FLU combined with VOR. AMB-d, amphotericin B deoxycholate; AMB-LF, lipid formulations of amphotericin B; CAS, caspofungin; MIC, micafungin; POS, posaconazole.

approximates the rates in prior studies reporting relatively recent outcomes and is likely to be a better estimate of attributable mortality. Improved contemporary outcomes likely reflect improved diagnostic and therapeutic modalities, compared with older patient series. In addition, it is likely that the potent and well-tolerated antifungal agents that are newly available have improved outcomes.

A number of host variables have been associated with both improved survival rates (e.g., nonmyeloablative conditioning regimens and use of peripheral blood as a stem cell source) and higher mortality (e.g., receipt of transplants from HLA-mismatched donors, neutropenia, abnormal renal function, elevated bilirubin level, and use of corticosteroids) in allogeneic HSCT recipients with IA [11, 14]. In our study, receipt of a nonmyeloablative conditioning regimen and absence of severe organ failure appeared to be protective in bivariate analyses of 6-week mortality risk factors for allogeneic HSCT recipients with IA. Of note, only the absence of severe organ dysfunction >40 days after transplantation was significantly associated with improved outcome ($P = .02$), perhaps because of the small number of patients included in these analyses.

More than one-half of the patients we describe were enrolled by only 2 institutions; this may have skewed the presented outcomes and created further biases. For instance, almost one-half of the allogeneic HSCT recipients described in this study came from a single institution. When secondary survival analyses were performed that excluded the 93 patients who presented to that center, survival outcomes were similar to those observed in the overall patient population (data not shown). The majority of autologous HSCT recipients with an IFI (50 [68.5%] of 73 patients) were reported by a single center. Autologous HSCT recipients in this study had received a diagnosis of multiple myeloma (68.5%), had experienced a relapse of their underlying disease (60.3%), had a history of prior HSCT (56.2%), and had received corticosteroids (75.3%). This, in part, may have had an impact on the high number of cases of IA and the associated high mortality rate observed among autologous HSCT recipients in our study [15, 16]. Although differences in patient risks may, in part, explain this finding, there are obviously differences in clinical approaches and diagnostic aggressiveness between transplantation centers; these factors should be addressed in the design and conduct of future registries and clinical trials.

Although the frequency of IA remained relatively stable during 2005–2006, there seemed to be a trend toward higher numbers of IFIs due to Zygomycetes and other molds. This trend, first described in patients who received transplants after 1995, probably reflects the higher-risk transplantations performed (leading to a more immunosuppressed patient population) and the extensive use of prophylactic treatment with agents that have activity against *Aspergillus* species (e.g., voriconazole) [4, 9]. Availability of voriconazole as a therapeutic agent may also lead to diagnostic "bias," with innately resistant infections (zygomycosis) being diagnosed today; these infections may have been treated empirically with amphotericin B products in the 1990s. Of note, conventional amphotericin B was minimally used in this study. Because this reflects the practice observed in 16 different medical centers, it appears that conventional amphotericin B has largely been replaced by the lipid formulations of amphotericin B and the new third-generation azoles.

A shift toward late diagnosis of IA (i.e., >40 days after HSCT) among allogeneic HSCT recipients has been reported by multiple centers [3, 17, 18]. Almost two-thirds of IA cases among allogeneic HSCT recipients in this study were observed >40 days after transplantation. However, a number of IA cases among recipients of allogeneic (37.1%) and autologous (48.9%) HSCTs were observed ≤40 days after transplantation. This suggests that IA remains a significant problem soon after trans-

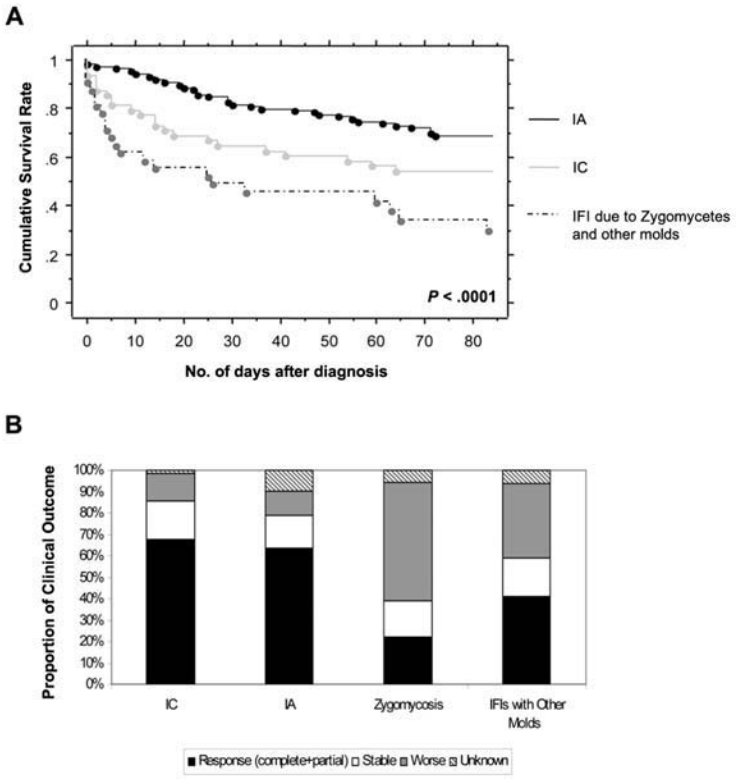

Figure 4. *A,* Twelve-week survival outcome for invasive fungal infection (IFI) in patients with 1 IFI; *P* value is calculated by log-rank test. *B,* Investigator-judged response to therapy for IFI in hematopoietic stem cell transplant recipients 12 weeks after transplantation. IA, invasive aspergillosis; IC, invasive candidiasis.

plantation, despite the routine administration of prophylactic therapy and the aggressive monitoring of these patients. In accordance with already published data [9], we found that IFI due to Zygomycetes or other molds remains a later complication for both allogeneic and autologous HSCT recipients.

Although the majority of patients with IC responded to the administered treatment, IC was associated with a 12-week mortality rate of 48.9%. We believe that this most likely reflects the underlying compromised immune status and organ function of patients who develop *Candida* infection; the true attributable mortality rate is unclear in this registry. Because of the small number of patients with IC in our study, we were not able to obtain data on potential risk factors associated with mortality in HSCT recipients with IC. IFIs due to Zygomycetes or other molds were associated with the highest mortality rates in our study (64.3% and 80.0%, respectively). This may be the result of the cumbersome, occasionally late diagnosis and suboptimal therapeutic modalities available for the management of these infections. Clearly, more studies need to be performed that address the diagnostic approaches to and treatment of IFI due to molds other than *Aspergillus* species.

This study has a number of limitations. Because of the design of this registry, the total number of transplants performed at each center is not recorded; thus, the incidences of the different IFIs cannot be calculated. Although this is a prospective data collection registry, the database is observational in nature and subject to a number of potential biases. Although data on antifungal therapy administered ⩽30 days before diagnosis of the IFI were collected, it is not possible to clearly distinguish between prophylactic, preemptive, and empirical therapy. Information on supportive care of HSCT recipients at different centers was not available. In addition, information on the cytomegalovirus serostatus of donors and recipients was not reported. Finally, the results are limited to patients enrolled from selected centers in North America, and as such, they may not reflect practices from other parts of North America or around the globe.

Overall, we report that IA remains the most commonly identified IFI among HSCT recipients, although survival at 12 weeks has significantly improved. IFIs due to *Candida* species, Zygomycetes, and other molds were also observed and were associated with high mortality rates. As practices in the HSCT setting change, and as new diagnostic and therapeutic modalities are added to the armamentarium of clinicians, this field will continue to set challenges and require answers through future prospective, multiple-center studies.

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References

1. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. J Infect Dis **1995**; 171: 1545–52.
2. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood **2000**; 96:2055–61.
3. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood **2002**; 100:4358–66.
4. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis **2000**; 30: 851–6.
5. Post MJ, Lass-Floerl C, Gastl G, Nachbaur D. Invasive fungal infections in allogeneic and autologous stem cell transplant recipients: a single-center study of 166 transplanted patients. Transpl Infect Dis **2007**; 9: 189–95.
6. Pagano L, Caira M, Nosari A, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study—Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. Clin Infect Dis **2007**; 45:1161–70.
7. Horn DL, Fishman JA, Steinbach WJ, et al. Presentation of the PATH alliance® registry for prospective data collection and analysis of the epidemiology, therapy, and outcomes of invasive fungal infections. Diagn Microbiol Infect Dis **2007**; 59:407–14.
8. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis **2002**; 34:7–14.
9. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis **2002**; 34:909–17.
10. Cordonnier C, Ribaud P, Herbrecht R, et al. Prognostic factors for death due to invasive aspergillosis after hematopoietic stem cell transplantation: a 1-year retrospective study of consecutive patients at French transplantation centers. Clin Infect Dis **2006**; 42:955–63.
11. Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. Clin Infect Dis **2007**; 44: 531–40.
12. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med **2002**; 347:408–15.
13. Wingard JR, Ribaud P, Schlamm HT, Herbrecht R. Changes in causes of death over time after treatment for invasive aspergillosis. Cancer **2008**; 112:2309–12.
14. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood **2003**; 102: 827–33.
15. Crippa F, Holmberg L, Carter RA, et al. Infectious complications after autologous CD34-selected peripheral blood stem cell transplantation. Biol Blood Marrow Transplant **2002**; 8:281–9.
16. Jantunen E, Salonen J, Juvonen E, et al. Invasive fungal infections in autologous stem cell transplant recipients: a nation-wide study of 1188 transplanted patients. Eur J Haematol **2004**; 73:174–8.
17. Grow WB, Moreb JS, Roque D, et al. Late onset of invasive aspergillus infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant **2002**; 29:15–9.
18. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis **1997**; 175:1459–66.

Administration of Voriconazole in Patients With Renal Dysfunction

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Background. The intravenous use of voriconazole requires coadministration with sulphobutylether-β-cyclodextrin, which may accumulate in patients with impaired renal function.

Methods. All adult patients treated with the same formulation of voriconazole for a minimum of 3 consecutive days were included. Renal function was assessed based on the creatinine level and the calculated creatinine clearance (CrCl). Change in renal function was calculated on days 3, 7, and end of treatment (EOT) and was defined based on the RIFLE criteria.

Results. Among 166 patients in whom baseline renal function was assessed, 42 (25.3%) had a CrCl <50 mL/min and received intravenous voriconazole, 77 (46.4%) had a CrCl ≥50 mL/min and received intravenous voriconazole, and 47 (28.3%) had a CrCl <50 mL/min and were treated with oral voriconazole. Renal function changed on days 3, 7, and EOT in 19 (11.4%), 14 (8.4%), and 28 (16.9%) patients, respectively. Multivariate analyses identified significant predictors of renal dysfunction: (1) day 3, hematologic malignancy (odds ratio [OR], 5.09, $P = .01$), fluconazole use within 30 days prior to voriconazole (OR, 6.21; $P = .008$), coadministration of penicillins (OR, 6.12; $P = .03$), and immunosuppressants (OR, 7.00; $P = .002$); (2) day 7, baseline liver impairment (OR, 5.30; P value = .004); (3) EOT, administration of penicillins (OR, 2.39; $P = .04$).

Conclusions. Voriconazole route of administration and baseline renal function were not predictors of worsening renal dysfunction on days 3, 7, and EOT. Underlying disease, baseline liver impairment, and concomitant administration of other drugs (eg, penicillins, fluoroquinolones, immunosuppressants) were the strongest predictors of renal dysfunction.

Voriconazole is a triazole used for prophylaxis and treatment of invasive fungal infections. The intravenous use of voriconazole requires coadministration with sulphobutylether-β-cyclodextrin (SBECD), which may accumulate in patients with impaired renal function. The voriconazole prescribing information defines patients with impaired renal function as having a creatinine level >2.5 mg/dL or creatinine clearance (CrCl) <50 mL/min [1, 2]. SBECD, which was developed as a solubilizing agent, is cleared at the glomerular filtration rate. Repeated dose models of SBECD administration to mice and rats yielded dose-related changes in kidney tissue pathology [3]. More specifically, administration of SBECD has been associated with kidney toxicity as a result of renal tubule vacuolation and obstruction in rat models [1, 3]. This appeared to be associated with SBECD administration at higher doses (mild toxicity in rat kidneys was observed with 3000 mg/kg, which is approximately 50-fold greater than the SBECD dose typically administered in humans, whereas doses up to 1500 mg/kg were not associated with any histopathological changes in dog kidneys) and for a longer duration (1–6 months) [1, 4]. Current guidelines suggest that voriconazole should

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not be administered intravenously to patients with renal impairment, including patients with CrCl <50 mL/min, or patients who require hemodialysis (HD) or continuous venovenous hemodiafiltration (CVVHD) [1, 2]. Instead, administration of voriconazole via the oral route is recommended in these cases. However, oral voriconazole has been associated with lower therapeutic drug levels, treatment failures, and the oral route may not be feasible in some situations [5, 6]. Henceforth, in cases of life-threatening invasive fungal infections, intravenous voriconazole administration may be warranted to ascertain adequate drug levels and optimize the clinical outcome, irrespective of renal dysfunction.

Limited data exist on the safety of intravenous voriconazole in patients with impaired renal function (CrCl <50 mL/min [7, 8] or requiring HD [4] or CVVHD [9–12]). Furthermore, Mohr et al reported that cyclodextrin can be eliminated by HD in patients treated with intravenous itraconazole [11]. In contrast, von Mach et al reported significant accumulation of cyclodextrin in 3 of 4 patients treated with intravenous voriconazole on HD, albeit without any differences observed in the voriconazole-associated adverse reactions [4]. Despite reports of accumulation, it is not clear that cyclodextrin itself actually harms the kidneys in humans [1, 3, 4, 8].

We hypothesized that intravenous voriconazole may be well tolerated in patients with impaired renal function and can be safely administered. This issue is critically important to resolve, given the known renal toxicities of compounds used as alternatives (eg, amphotericin products). We conducted a retrospective study at 2 academic medical centers in which we sought to assess changes in renal function of patients treated with intravenous or oral voriconazole for 3 days or more.

METHODS

The study was approved by the institutional review boards at The Johns Hopkins Hospital (JHH) and the University of Pittsburgh Medical Center (UPMC). This was a retrospective, observational study of adult (>18 years) patients who were treated with voriconazole using the same route of administration for a minimum of 3 consecutive days. The manufacturer and formulation of voriconazole remained consistent throughout the study period for both institutions and for both routes of administration (intravenous and oral). Patients were identified from the institutions' pharmacy databases. Exclusion criteria included prior administration of voriconazole within 30 days and requirements for HD or CVVHD. In an effort to include only high-risk patients for renal impairment, those with baseline CrCl >50 mL/min treated with oral voriconazole were also excluded. Renal function was assessed based on creatinine and calculated CrCl, using the Cockcroft-Gault formula. Change in renal function from baseline (day 1) was calculated on days 3 and 7 and at end of treatment (EOT) and was defined based on the RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease) proposed by the Acute Dialysis Quality Initiative Group [14]. More specifically, an increase in the serum creatinine >1.5 times baseline or/and a decrease in CrCl by >25% was considered a significant change in renal function [14]. Creatinine was measured with an enzymatic method (Roche Hitachi Modular Analyzer) at JHH and an alkaline picrate reaction at UPMC. Baseline liver impairment was defined as aspartate aminotransferase or alanine aminotransferase >3 times the upper normal limit or/and alkaline phosphatase >2 times the upper normal limit.

Data Collection

The following data were collected: demographics, weight, comorbidities (underlying malignancy, solid tumor or hematologic malignancy, diabetes mellitus, and cardiovascular disease), receipt of a solid organ or hematopoietic stem cell transplant (HSCT), HSCT-related variables (type of transplant, graft vs host disease, and associated treatments), requirement for mechanical ventilation, and administration of antifungal agents within 30 days prior to voriconazole initiation. The creatinine level and CrCl on days 1, 2, 3, and 7 and at EOT were collected. Liver function tests on day 1 (±3 days) were recorded. Concomitant administration of the following medications was collected: vasopressors, corticosteroids or other immunosuppressive agents, and antimicrobial agents (aminoglycosides, carbapenems, cephalosporins, colistin, fluoroquinolones, foscarnet, ganciclovir, penicillins, and vancomycin). For vancomycin, duration of administration and vancomycin level (random or trough) during the first 7 days of treatment were recorded when available. For voriconazole, the following variables were collected if available: indication (prophylaxis vs treatment), loading and maintenance dose, route and frequency of administration, start and stop day, and plasma levels.

Statistical Analysis

The primary objective of this study was to assess the rate of renal dysfunction among patients treated with voriconazole for a minimum of 3 and 7 consecutive days of administration of the same formulation of voriconazole. Using logistic regression models, we sought to identify risk factors for renal dysfunction among patients treated with voriconazole based on indicators of change in renal dysfunction between day 1 and day 3, day 7, and EOT. To specifically address the impact of intravenous voriconazole administration in patients with impaired renal dysfunction (CrCl <50 mL/min) on outcomes, the following variables were added to the univariate analysis: route of voriconazole administration (intravenous vs oral) and baseline renal

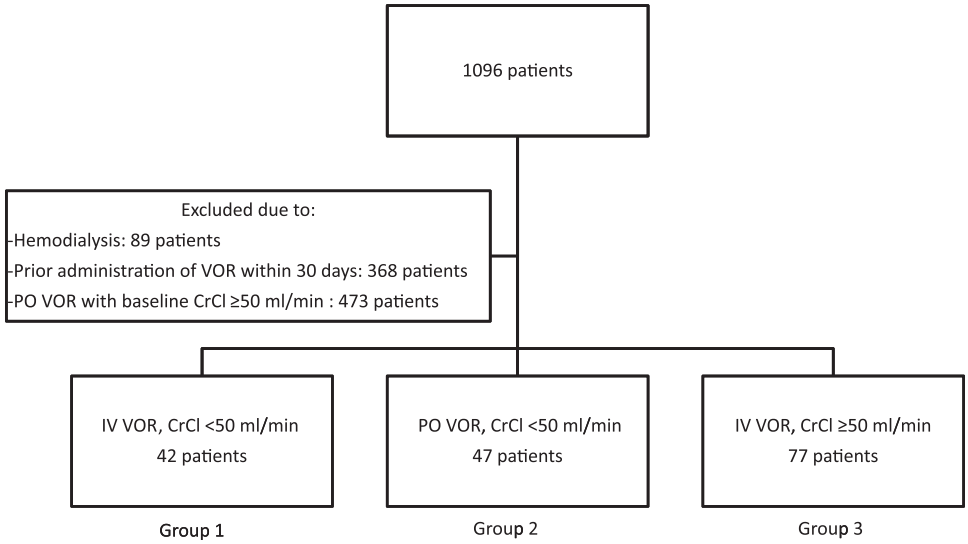

Figure 1. Distribution of patient population. Abbreviations: CrCl, creatinine clearance; IV, intravenous; PO, oral; VOR, voriconazole.

function (CrCl ≥50 mL/min vs CrCl <50 mL/min). In addition, patients were divided into group 1 (intravenous voriconazole with baseline CrCl <50 mL/min), group 2 (oral voriconazole and baseline CrCl <50 mL/min), and group 3 (intravenous voriconazole with baseline CrCl ≥50 mL/min), and pairwise group comparisons were made. Variables that had a *P* value ≤.20 in the univariate analyses were introduced into stepwise multivariate logistic regression models to assess risk factors for renal impairment progression adjusted for the other risk factors in the models.

A classification tree analysis was performed for each outcome to identify characteristics of patients with a greater likelihood of renal impairment progression based on the variables included in the multivariate analyses. These subsets were then compared with all other patients using logistic regression analyses to assess the impact of the characteristic combinations on renal impairment progression. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented for all logistic regression analysis results. Statistical analyses were performed using Stata software v 11.1 (StataCorp, College Station, Texas, 2010) and R v 2.11.1 (http://www.r-project.org/).

RESULTS

Baseline Patient Characteristics

A total of 1096 patients were identified who received the same formulation of voriconazole for more than 3 consecutive days. After excluding 930 patients, a total of 166 patients were included in the study population (Figure 1). The baseline patient characteristics are detailed in Table 1. Among 166 patients, 42 (25.3%) had a CrCl <50 mL/min and received intravenous voriconazole (group 1), 47 (28.3%) had a CrCl <50 mL/min and were treated with oral voriconazole (group 2), and 77 (46.4%) had a CrCl ≥50 mL/min and received intravenous voriconazole (group 3). A total of 109 (65.7%) patients received loading doses of voriconazole at 6 mg/kg twice daily for 1 day. Information on maintenance dose of voriconazole was available for all patients: 47 (28.3%) received a standard dose of 200 mg twice daily, 35 (21.1%) received 2–3 mg/kg twice daily, 72 (43.4%) received 4 mg/kg twice daily, and 12 (7.2%) received 5–6 mg/kg twice daily. Median duration of treatment with voriconazole was 10 days (range, 3–25), 10 days (range, 3–59), and 9 days (range, 2–86) for groups 1, 2, and 3, respectively. Plasma voriconazole levels were available for 27 (16.3%) patients (n = 10, 5, and 12 for groups 1, 2, and 3, respectively). Eight (29.6%) patients had a level ≥5 μg/mL: 2 (20%), 1 (20%), and 5 (41.7%) patients in groups 1, 2, and 3, respectively. Patients in group 2 were less likely to have received a loading dose of voriconazole (15 of 47, 31.9%; $P < .0001$) and more likely to have received voriconazole as prophylaxis (28, 59.9%; $P = .002$), a solid organ transplant (23, 48.9%; $P = .007$), and immunosuppressive agents (25, 53.2%; $P = .02$) compared with the other 2 groups.

The mean (95% CI) creatinine for group 1 on days 1, 3, 7, and EOT was 1.93 (1.75–2.11), 1.93 (1.68–2.18; $P = .98$), 1.55 (1.27–1.83; $P = .02$), and 1.84 (1.57–2.11; $P = .52$), respectively, where *P* values are for the comparison of day 1 to the other 3 time points (Figure 2). The mean (95% CI) creatinine for group 2 on days 1, 3, 7, and EOT was 2.14 (1.93–2.36), 2.19 (1.90–2.47; $P = .65$), 2.07 (1.67–2.48; $P = .62$), and 2.02 (1.63–2.42; $P = .36$), respectively. The mean (95% CI) creatinine for group 3 on days 1, 7, and EOT was 0.87 (.79–.94), 0.93

Table 1. Baseline Patient Characteristics for the Overall Study Population and by Group Patient Category

Variables	All Study Patients (n = 166), No. (%)	Group 1 (n = 42), No. (%)	Group 2 (n = 47), No. (%)	Group 3 (n = 77), No. (%)	*P* Value
Demographics					
Age, mean, years (range)	52.8 (19–90)	57.3 (20–90)	56.5 (32–81)	48 (19–84)	<.05
Sex, female	78 (47)	23 (54.8)	24 (51.1)	31 (40.3)	.25
Ethnicity, white	143 (86.1)	35 (83.3)	44 (93.6)	64 (83.1)	.21
Voriconazole-related variables					
Loading dose	109 (65.7)	32 (76.2)	15 (31.9)	62 (80.5)	<.0001
Maintenance dose, ≤4 mg/kg twice daily[a]	154 (92.8)	36 (85.7)	46 (97.9)	72 (93.5)	.08
Days, ≤7 days	73 (44.0)	20 (47.6)	17 (36.2)	36 (46.7)	.44
Indication, prophylaxis	63 (37.9)	12 (28.6)	28 (59.5)	23 (29.9)	.002
Host-related variables					
Baseline liver impairment[b]	32 (19.3)	9 (21.9)	10 (21.7)	13 (17.3)	.97
Diabetes mellitus	48 (28.9)	16 (38.1)	15 (31.9)	17 (22.1)	.16
Cardiovascular disorder	70 (42.2)	19 (45.2)	24 (51.1)	27 (35.1)	.19
Solid tumor	26 (15.7)	6 (14.3)	5 (10.6)	15 (19.5)	.40
Hematologic malignancy	63 (37.9)	14 (33.3)	19 (40.2)	30 (38.9)	.76
Hematopoietic stem cell transplant	20 (12.0)	5 (11.9)	4 (8.5)	11 (14.3)	.63
Solid organ transplant	56 (33.7)	16 (38.1)	23 (48.9)	17 (22.1)	.007
Prior antifungal agents[c]	74 (44.6)	24 (53.1)	17 (36.2)	33 (42.9)	.13
Fluconazole	40 (54.1)	17 (40.5)	6 (12.8)	17 (22.1)	.008
Amphotericin B	34 (45.9)	8 (19.0)	11 (23.4)	15 (19.5)	.84
Antibacterial agents[d]	155 (93.4)	36 (85.7)	46 (97.9)	73 (94.8)	.06
Penicillins	73 (47.1)	16 (38.1)	24 (51.1)	33 (42.9)	.45
Cephalosporins	33 (21.3)	5 (11.9)	9 (19.1)	19 (24.7)	.25
Carbapenems	30 (19.4)	8 (19.0)	6 (12.7)	16 (20.8)	. 52
Fluoroquinolones	55 (35.5)	8 (19.0)	18 (38.3)	29 (37.7)	.08
Vancomycin	97 (62.6)	25 (59.5)	27 (57.4)	45 (58.4)	.90
Duration of vancomycin therapy (≥7 days)	47 (48.4)	7 (28.0)	12 (44.4)	28 (62.2)	.02
Vancomycin level ≥20 mcg/mL[e]	33 (40.2)	12 (54.5)	10 (45.4)	11 (28.9)	.13
Aminoglycosides	11 (7.1)	2 (4.8)	3 (6.4)	6 (7.8)	.77
Vasopressive agents[d]	40 (24.1)	12 (28.6)	8 (17.0)	20 (26.0)	.39
Immunosuppressive agents[d]	63 (37.9)	16 (38.1)	25 (53.2)	22 (28.6)	.02
Corticosteroids[d]	89 (53.6)	25 (59.5)	26 (55.3)	38 (49.3)	.55
Mechanical ventilation	63 (37.9)	14 (33.3)	15 (31.9)	34 (44.1)	.31

Group categories: group 1 (intravenous voriconazole [VOR] with baseline creatinine clearance [CrCl] <50 mL/min), group 2 (oral voriconazole and baseline CrCl <50 mL/min), and group 3 (intravenous voriconazole with baseline CrCl ≥50 mL/min).

[a] Maintenance dose ≤4 mg/kg twice a day included: n = 47 (group 1, n = 10; group 2, n = 25; group 3, n = 12) with 200 mg twice a day, n = 35 (group 1, n = 7; group 2, n = 15; group 3, n = 13) with 2–3 mg/kg twice a day, and n = 72 (group 1, n = 19; group 2, n = 6; group 3, n = 47) with 4 mg/kg twice a day. A total of n = 12 (group 1, n = 6; group 2, n = 1; group 3, n = 5) received >4 mg/kg twice a day.

[b] Defined as any of the following: aspartate aminotransferase or alanine aminotransferase >3 times the upper normal limit and/or alkaline phosphatase >2 times the upper normal limit, obtained ±3 days of VOR initiation. Data were available for 162 patients (group 1, n = 41; group 2, n = 46; group 3, n = 75).

[c] Any antifungal agents administered within 30 days prior to VOR initiation.

[d] Administered concomitantly with VOR.

[e] Vancomycin trough or random level ≥20 mcg/mL at least once during the first 7 days of vancomycin administration. Vancomycin level was available for 82 patients (group 1, n = 22; group 2, n = 22; group 3, n = 38).

(.84–1.02; $P = .01$), 0.92 (.76–1.07; $P = .21$), and 1.02 (.84–1.20; $P = .06$), respectively.

Risk Factor Analysis for Renal Dysfunction

Using the RIFLE criteria based on glomerular filtration rate or creatinine level [14], a change in renal function on days 3, 7, and EOT was observed in 19 (11.4%), 14 (8.4%), and 28 (16.9%) patients, respectively. Univariate analyses to identify risk factors for renal dysfunction on days 3, 7, and EOT were performed using the variables presented in Table 2. Variables with a *P* value ≤ .20 on days 3, 7, and EOT were introduced in 3 respective stepwise multivariate logistic regression models

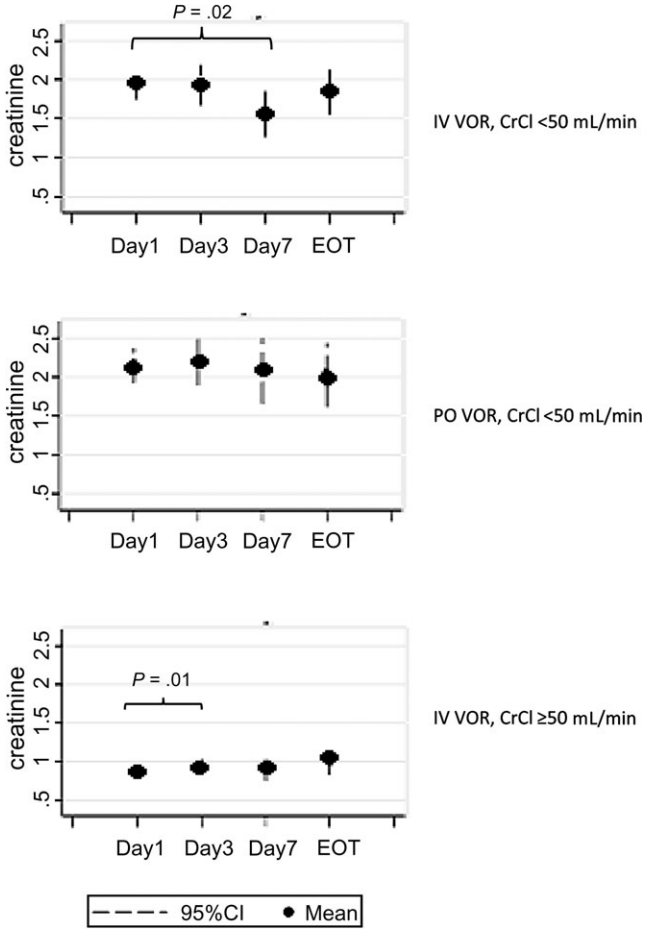

Figure 2. Comparison of creatinine levels versus time for patients with intravenous (IV) voriconazole (VOR) and creatinine clearance (CrCl) <50 mL/min, oral (PO) VOR and CrCl <50 mL/min, and IV VOR and CrCl ≥50 mL/min. *P* values are presented only for those changes with $P < .05$. Abbreviations: CI, confidence interval; EOT, end of treatment.

(Table 3). For day 3, a history of hematologic malignancy (OR, 5.09 [95% CI, 1.38–18.73]; $P = .01$), fluconazole use within 30 days prior to voriconazole (OR, 6.21 [95% CI, 1.62–23.77]; $P = .008$), and coadministration of penicillins (OR, 6.12 [95% CI, 1.24–30.05]; $P = .03$) and immunosuppressants (OR, 7.00 [95% CI: 2.02–24.28]; $P = .002$) were the most significant predictors of renal dysfunction. In contrast, administration of voriconazole for >7 days (OR, 0.19 [95% CI, .05–.69]; $P = .01$) and coadministration of vasopressors (OR, 0.13 [95% CI, .02–.77]; $P = .02$) were found to be protective of renal dysfunction. Baseline liver impairment was the only significant predictor of renal dysfunction on day 7 (OR, 5.30 [95% CI, 1.69–16.52]; $P = .004$). For EOT, administration of penicillins was a significant predictor of renal dysfunction at EOT (OR, 2.39 [95% CI, 1.01–5.66]; $P = .04$), while white ethnicity appeared to be protective (OR, 0.36 [95% CI, 0.13–0.99]; $P = .04$).

Classification Tree Analysis (Figure 3)

For day 3, renal dysfunction was more likely to happen in the following groups: (1) patients who received voriconazole for ≤7 days, penicillins, and fluoroquinolones (OR, 30.7 [95% CI, 6.04–156.11]; $P < .0001$); (2) patients treated with immunosuppressive agents who received voriconazole for ≤7 days but not penicillins or vasopressors (OR, 7.90 [95% CI, 1.66–37.45]; $P = .009$), and (3) patients treated with voriconazole for >7 days who received fluconazole within 30 days prior to voriconazole administration and had a hematologic malignancy (OR, 7.80 [95% CI, 2.47–44.86]; $P = .001$). For day 7, baseline liver impairment was the primary determinant of renal dysfunction with the following groups being at higher risk: (1) patients with baseline liver impairment and normal renal function (CrCl >50 mL/min) who received penicillins (OR, 47 [95% CI, 8.66–255.13]; $P < .0001$), (2) patients with baseline liver and renal (CrCl ≤50 mL/min) impairment and concomitant administration of penicillins and voriconazole for ≤7 days (OR, 14.1 [95% CI, 2.06–96.49]; $P = .007$), and (3) patients without liver impairment who received voriconazole for >7 days and were treated with vasopressors but not vancomycin (OR, 18.8 [95% CI, 2.53–139.65]; $P = .004$). For EOT, administration of penicillins and ethnicity were the primary determinants, with the following 2 groups at higher risk for renal dysfunction: (1) non-Caucasian patients treated with penicillins (OR, 8.6 [95% CI, 2.20–35.23]; $P = .003$) and (2) Caucasian patients with baseline liver impairment treated with penicillins (OR, 3.4 [95% CI, 1.05–11.27]; $P = .04$).

DISCUSSION

This is a retrospective observational study that reviewed the renal function of patients treated with voriconazole for a minimum of 3 consecutive days with the same mode of administration. Using predefined criteria to assess significant changes in renal function, the observed rates of change in renal function on days 3, 7, and EOT were 19 (11.4%), 14 (8.4%), and 28 (16.9%) patients, respectively. Based on our findings, baseline renal dysfunction, route of voriconazole administration, or a combination of the above did not impact renal impairment after 3 or 7 consecutive days of administration or at the EOT. In contrast, underlying disease, baseline liver impairment, and concomitant administration of other drugs (eg, penicillins, fluoroquinolones, immunosuppressants) were the strongest predictors of renal dysfunction.

Administration of fluconazole within 30 days prior to initiation of voriconazole and concomitant administration of penicillins were identified as major risk factors for renal dysfunction by day 3. As fluconazole and penicillin derivatives are not considered particularly nephrotoxic, we believe that they likely represent an indirect marker of disease severity

Table 2. Univariate Analyses of Risk Factors for Renal Dysfunction on Days 3 and 7 and at End of Treatment of Voriconazole[a]

	Day 3		Day 7		End of Treatment	
Predictor	Odds Ratio	*P* Value	Odds Ratio	*P* Value	Odds Ratio	*P* Value
Host-related variables						
Baseline renal function, CrCl > vs ≤50 mL/min	0.95	.93	0.45	.17	0.59	.21
Groups 2 and 3 vs group 1	1.31	.65	1.26	.73	1.02	.97
Age, ≥50 vs <50 years	1.33	.58	1.08	.89	1.32	.53
Sex, female vs male	2.1	.14	0.60	.38	0.69	.37
Ethnicity, white vs other	0.56	.34	0.56	.40	0.39	.07
Baseline liver dysfunction[b], yes vs no	1.59	.41	5.08	.005	1.90	.18
Mechanical ventilation, yes vs no	1.55	.37	2.35	.13	1.28	.56
Diabetes mellitus, yes vs no	0.86	.79	1.96	.24	1.20	.68
Cardiovascular disease, yes vs no	1.27	.63	1.03	.96	1.23	.62
Solid tumor, yes vs no	2.14	.18	0.89	.88	1.21	.73
Hematologic malignancy, yes vs no	1.97	.17	1.25	.69	1.28	.56
HSCT, yes vs no	2.18	.21	1.25	.69	1.28	.56
SOT, yes vs no	1.17	.76	1.53	.45	1.11	.11
Voriconazole-associated variables						
Route of administration, intravenous vs oral	0.84	.74	2.52	.24	2.01	.19
Loading dose VOR, yes vs no	1.15	.79	0.94	.91	1.38	.48
Maintenance dose VOR, > vs ≤4 mg/kg twice/d	0.69	.73	0.99	.99	0.98	.98
Duration of VOR administration, > vs ≤7 days	0.40	.07	3.00	.10	0.85	.69
VOR indication, prophylaxis vs treatment	1.20	.71	0.89	.84	0.94	.89
VOR level[c], ≥5 vs <5 μg/mL	NA	NA	8.0	.2	18	.02
Other medication-associated variables						
Prior antifungal agent[d], yes vs no	0.89	.82	0.93	.89	0.92	.84
Fluconazole	2.61	.06	0.85	.81	1.06	.90
Amphotericin B	1.04	.95	1.63	.44	1.07	.89
Concomitant antibacterial agents[e], yes vs no	1.31	.80	0.91	.94	0.91	.90
Penicillins	2.41	.08	2.48	.12	2.26	.05
Cephalosporins	0.73	.64	1.70	.40	0.63	.42
Carbapenems	0.83	.78	1.26	.73	0.98	.97
Fluoroquinolones	1.98	.17	0.52	.34	1.66	.23
Aminoglycosides	NA	NA	1.09	.94	1.95	.35
Vancomycin	1.25	.66	0.36	.08	1.12	.79
Vancomycin with any of the above	1.43	.47	0.53	.27	1.68	.22
Vancomycin, > vs ≤3 concomitant days	0.24	.03	NA	NA	0.44	.13
Vancomycin level, <20 mcg/mL[f]	0.72	.66	1.52	.69	0.54	.34
Vasopressive agents[d], yes vs no	0.34	.16	2.60	.10	0.64	.40
Immunosuppressive agents[d], yes vs no	1.97	.17	1.25	.69	1.53	.31

Abbreviations: CrCl, creatinine clearance; HSCT, hematopoietic stem cell transplantation; NA, not applicable; SOT, solid organ transplantation; VOR, voriconazole.

[a] Variables with *P* values ≤ .20 were introduced in multivariate regression models.

[b] Defined as any of the following: aspartate aminotransferase or alanine aminotransferase >3 times the upper normal limit and/or alkaline phosphatase >2 times the upper normal limit.

[c] Voriconazole level was available for 27 patients.

[d] Antifungal agents administered within 30 days prior to voriconazole initiation.

[e] Agents administered concomitantly with voriconazole.

[f] Vancomycin trough or random level ≥20 mcg/mL at least once during the first 7 days of vancomycin administration.

rather than a direct kidney toxic agent and may have been more routinely administered to higher-risk patients. Patients with an underlying hematologic malignancy were at higher risk of developing renal dysfunction, perhaps as a result of their underlying immunocompromized status and administration of other nephrotoxic compounds including chemotherapeutic

Table 3. Multivariate Analysis Results on Risk Factors for Renal Dysfunction on Days 3 and 7 and at End of Treatment of Voriconazole Among 166 Patients Treated With Voriconazole and Available Data[a]

	Day 3		Day 7		End of Treatment	
Predictor	Odds Ratio	*P* Value	Odds Ratio	*P* Value	Odds Ratio	*P* Value
Ethnicity, white vs non-white	NS	NS	NS	NS	0.36	0.04
Hematologic malignancy	5.09	0.01	NS	NS	NS	NS
Fluconazole (within 30 days prior to VOR)	6.21	0.008	NS	NS	NS	NS
Baseline liver impairment[b]	NS	NS	5.30	0.004	NS	NS
Duration of VOR administration, > vs ≤7 days	0.19	0.01	NS	NS	NS	NS
Penicillins	6.12	0.03	NS	NS	2.39	0.04
Immunosuppressive agents	7.00	0.002	NS	NS	NS	NS
Vasopressive agents	0.13	0.02	NS	NS	NS	NS

Abbreviations: NS, not significant; VOR, voriconazole.

[a] Only variables with a $P < .20$ in univariate analyses were introduced in the multivariate analysis models.

[b] Defined as any of the following: aspartate aminotransferase or alanine aminotransferase >3 times the upper normal limit and/or alkaline phosphatase >2 times the upper normal limit.

agents. The effect of immunosuppressive agents on renal function has been clearly demonstrated, particularly in transplant recipients [15, 16]. In this study, it was not possible to discern whether immunosuppressants led to higher rates of renal dysfunction due to their direct nephrotoxic effect or were just a marker of disease severity.

Baseline liver impairment was the strongest predictor of renal impairment in patients treated with voriconazole for at least 7 consecutive days. Baseline liver dysfunction is likely to be an indirect marker of disease severity, suggesting that sicker patients (also requiring treatment with penicillin derivatives) may be at higher risk for developing renal dysfunction. In addition, liver dysfunction may lead to impaired metabolism of other concomitantly administered drugs with potential nephrotoxicity or/and affect renal function via other physiologic pathways. For instance, it has been hypothesized that the renin-angiotensin system stimulation due to liver disease may be the mechanism for development of nephrotoxicity in patients treated with aminoglycosides [17]. The impact of liver impairment on renal function was further confirmed with tree classification analyses that demonstrated liver impairment (and administration of penicillins) to be the strongest predictors of renal dysfunction regardless of baseline renal function.

Multivariate analysis at EOT demonstrated that administration of penicillins was the most significant predictor of renal dysfunction, while Caucasian ethnicity was protective. These results were further confirmed by tree classification analyses showing that non-whites treated with penicillins were more likely to develop renal dysfunction. Although penicillin derivatives have been associated with acute interstitial nephritis, we believe that this association may, in part, imply that patients requiring courses of penicillin drugs might have been sicker (as an indirect marker of disease severity) and hence more likely to develop renal impairment. In fact, white patients with baseline liver impairment treated with penicillins appeared to be at high risk for renal function deterioration. Consistent with prior reports, we observed that non-whites were more susceptible to such changes, perhaps associated with higher rates of hypertension and diabetes mellitus or genetic factors [18–21].

In univariate analyses, voriconazole blood level ≥5.0 mcg/mL was found to be significantly associated with worsening renal function at EOT. Voriconazole levels were available for only 27 patients, limiting our ability to make definitive conclusions. As voriconazole is extensively metabolized in the liver, hepatic impairment may lead to higher concentrations of voriconazole and associated toxicities. An elevated voriconazole level has been associated with increases in total bilirubin, aspartate aminotransferase, and alkaline phosphatase [22–26]. To our knowledge, creatinine and voriconazole level have been correlated in 1 study, although creatinine did not retain statistical significance in multivariate analyses [27].

Administration of vancomycin for ≥7 days and vancomycin levels ≥15 mcg/mL have been strongly associated with renal dysfunction [28–31]. Renal dysfunction was not associated with vancomycin use, duration of vancomycin administration, and high vancomycin levels (≥20 mcg/mL) in this study. Although more than half of the patients received vancomycin concomitantly with voriconazole, the effect of vancomycin on renal function might have been diluted due to the overall small number of patients included and stronger associations with other variables. In addition, vancomycin levels were available for a minority of patients only, which prevented preventing us from making further conclusions.

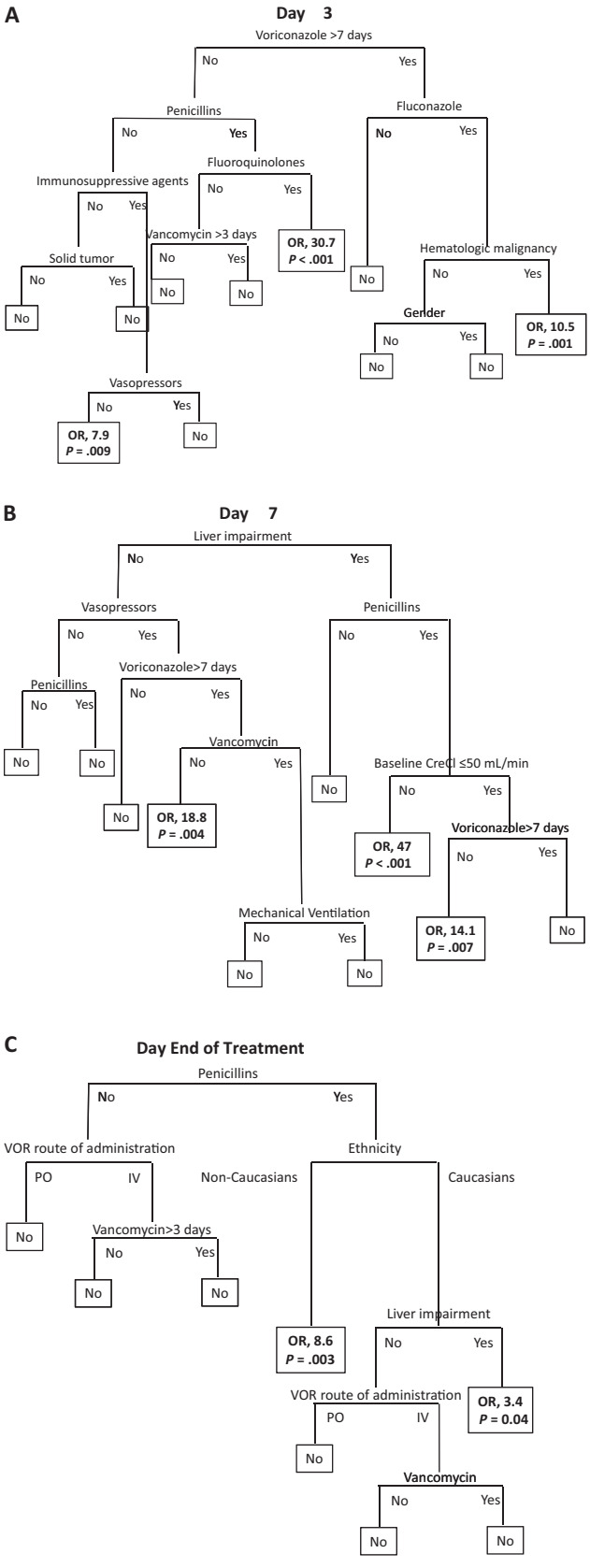

Figure 3. Classification tree prediction models for day 3 (*A*), day 7 (*B*), and end of treatment (*C*). Subsets of patients with higher likelihoods of renal dysfunction were compared with all other patients to identify the strength of the combined characteristics. A classification tree analysis was performed for each outcome to identify characteristics of patients with a greater likelihood of renal impairment progression based on the variables included in the multivariate analyses. These subsets were then compared with all other patients using logistic regression analyses to assess the impact of the characteristic combinations on renal impairment progression. In the classification tree analysis diagrams, the terminal nodes are portrayed by rectangles. Only the statistically significant terminal nodes are presented in this figure with the associated odds ratios and *P* values for renal dysfunction. *A*, The classification tree had a total of 25 nodes (13 were terminal nodes), and 10 major predictors were selected. The first level of the tree was split into 2 initial branches based on the duration of voriconazole administration, which was the best predictor of renal dysfunction. *B*, The classification tree had a total of 19 nodes (10 were terminal nodes), and 8 major predictors were selected. The first level of the tree was split into 2 initial branches according to baseline liver impairment, which was the best predictor of renal dysfunction. *C*, The classification tree had a total of 15 nodes (8 were terminal nodes), and 7 major predictors were selected. The first level of the tree was split into 2 initial branches according to administration of penicillins, which was the best predictor of renal dysfunction. Abbreviations: CreCl, creatine clearance; IV, intravenous; OR, odds ratio; PO, oral; VOR, voriconazole.

A major limitation of this study was the small number of patients included. Patients were not comparable in terms of several characteristics across the 3 groups to allow for more in-depth analyses. Hence, the observed results may be skewed due to the small number of patients included and may underrepresent all 3 groups. A limited number of patients continued voriconazole for ≥7 days, preventing us from making any significant conclusions for that time endpoint. It is likely that longer voriconazole courses may lead to cyclodextrin accumulation; albeit, we were not able to assess this effect in our study. Finally, different assays were used for creatinine measurement in the institutions involved in this study. As the alkaline picrate reaction has a variance structure, this assay may have more interference and lead to less accurate results.

In conclusion, we report that a small subset of patients treated with voriconazole develop renal dysfunction. We did not observe an impact of administration of intravenous voriconazole in patients with baseline CrCl <50 mL/min on deterioration of renal function after 3 or 7 consecutive days of administration. Although clinicians should be cautious when treating patients with renal dysfunction with intravenous voriconazole, weighing the risks and benefits of such an intervention is usually made at the bedside while considering a multitude of variables including the severity of infection being treated and general state and prognosis of the patient. Prospective studies will be required to definitively address the impact of intravenous voriconazole on the kidneys in patients with impaired renal function.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Food and Drug Administration. Antiviral Drugs Advisory Committee/ briefing document for voriconazole (oral and intravenous formulations). Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_01_Pfizer.pdf. Accessed 31 July 2011.
2. Food and Drug Administration. Background document for the Antiviral Drug Products Advisory Committee meeting. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_02_FDA-voriconazole.htm. Accessed 31 July 2011.
3. Luke DR, Tomaszewski K, Damle B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). J Pharm Sci **2010**; 99:3291–301. Accessed 31 July 2011.
4. von Mach MA, Burhenne J, Weilemann LS. Accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium in critically ill patients treated with intravenous voriconazole under renal replacement therapy. BMC Clin Pharmacol **2006**; 6:6.
5. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis **2008**; 46:201–11.
6. Trifilio S, Pennick G, Pi J, et al. Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. Cancer **2007**; 109:1532–5.
7. Abel S, Allan R, Gandelman K, Tomaszewski K, Webb DJ, Wood ND. Pharmacokinetics, safety and tolerance of voriconazole in renally impaired subjects: two prospective, multicentre, open-label, parallel-group volunteer studies. Clin Drug Investig **2008**; 28:409–20.
8. Potoski BA, Sima AP. Effect of intravenous voriconazole on serum creatinine in a population of patients with stable renal dysfunction. In: IDSA-ICAAC Annual Meeting, 25–28 October 2008. Washington, DC. Abstract A-018.
9. Robatel C, Rusca M, Padoin C, Marchetti O, Liaudet L, Buclin T. Disposition of voriconazole during continuous veno-venous haemodiafiltration (CVVHDF) in a single patient. J Antimicrob Chemother **2004**; 54:269–70.
10. Fuhrmann V, Schenk P, Jaeger W, et al. Pharmacokinetics of voriconazole during continuous venovenous haemodiafiltration. J Antimicrob Chemother **2007**; 60:1085–90.
11. Mohr JF, Finkel KW, Rex JH, Rodriguez JR, Leitz GJ, Ostrosky-Zeichner L. Pharmacokinetics of intravenous itraconazole in stable hemodialysis patients. Antimicrob Agents Chemother **2004**; 48:3151–3.
12. Hafner V, Czock D, Burhenne J, et al. Pharmacokinetics of sulfobutylether-beta-cyclodextrin and voriconazole in patients with end-stage renal failure during treatment with two hemodialysis systems and hemodiafiltration. Antimicrob Agents Chemother **2010**; 54:2596–602.
13. Burkhardt O, Thon S, Burhenne J, Welte T, Kielstein JT. Sulphobutylether-beta-cyclodextrin accumulation in critically ill patients with acute kidney injury treated with intravenous voriconazole under extended daily dialysis. Int J Antimicrob Agents **2010**; 36:93–4.
14. Bellomo R, Ronco C, Kellum JA, et al. Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care **2007**; 11:411.
15. de Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: long-term consequences and challenges for the future. Am J Kidney Dis **2000**; 35:333.
16. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol **2009**; 4:481.
17. Moore R, Smith C, Lipsjy J, Mellits ED, Lietman PS. Risk factors for nephrotoxicity in patients treated with aminoglycosides. Ann Intern Med **1984**; 100:352–7.
18. Peralta CA, Shlipak MG, Fan D, et al. Risks for end-stage renal disease, cardiovascular events, and death in Hispanic versus non-Hispanic white adults with chronic kidney disease. J Am Soc Nephrol **2006**; 17:2892.
19. United States Renal Data System 2009 Annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, **2009.** Available at: http://www.usrds.org/adr.htm. (Accessed 20 August 2011).
20. Tareen N, Zadshir A, Martins D, Pan D, Nicholas S, Norris K. Chronic kidney disease in African American and Mexican American populations. Kidney Int Suppl **2005**; 97:S78–81.
21. Hsu CY, Lin F, Vittinghoff E, Shlipak MG. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. J Am Soc Nephrol **2003**; 14:2902.
22. Johnson HJ, Han K, Capitano B, et al. Voriconazole pharmacokinetics in liver transplant recipients. Antimicrob Agents Chemother **2010**; 54: 852–9.
23. Amigues I, Cohen N, Chung D, et al. Hepatic safety of voriconazole after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2010**; 16:46–52.
24. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. J Clin Pharmacol **2006**; 46:235–43.
25. Food and Drug Administration. Briefing document for voriconazole. 2001. Available at: http://www.fda.gov/ohrms/DOCKETS/ac/01/briefing/3792b2_01_Pfizer.pdf (Accessed 1 July 2009).
26. Trifilio S, Ortiz R, Pennick G, et al. Voriconazole therapeutic drug monitoring in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant **2005**; 35:509–13.
27. Lombardi L, Miano T, Davis J, et al. A retrospective analysis of the effect of patient-specific factors on voriconazole concentrations in oncology patients. J Oncol Pharm Pract **2011**; 97:S78–81.
28. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis **2009**; 49:507–14.
29. Pritchard L, Baker C, Leggett J, Sehgev P, Brown A, Bayley KB. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. Amer J Medic **2001**; 123:1143–9.
30. Hermsen E, Hanson M, Sankaranarayanan J, Stoner JA, Florescu MC, Rupp ME. Clinical outcomes and nephrotoxicity associated with vancomycin trough concentrations during treatment of deep-seated infections. Expert Opin Drug Saf **2010**; 9:9–14.
31. Jeffres M, Isakow W, Doherty J, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care–associated methicillin-resistant *Staphylococcus aureus* pneumonia. Clin Ther **2007**; 29:1107–15.

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Original Article

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Reasons for voriconazole prophylaxis discontinuation in allogeneic hematopoietic cell transplant recipients: A real-life paradigm

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Abstract

We sought to describe the clinical experience of voriconazole as primary antifungal prophylaxis (AFP) in allogeneic hematopoietic cell transplant recipients (allo-HCTr). This was a single-center retrospective study of adult allo-HCTr (1 January 2014 to 31 December 2016) who received ≥two doses of voriconazole-AFP. Voriconazole-AFP was started on day +7 post-HCT and continued at least through day +60 post-HCT, or longer as clinically indicated. We reviewed the rate, reasons, and risk factors of voriconazole-AFP discontinuation until day-100 post-HCT. A total of 327 patients were included. Voriconazole-AFP was continued for a median of 69 days (mean: 57.9; range 1, 100): for a median of 90 days (mean :84; range 2, 100) in 180/327 (55%) in the standard-of-care (SOC) group and 20 days (mean :25.6 ; range 1, 89; *P*-value < .001) in 147/327 (45%) patients in the early-discontinuation-group. Early-voriconazole-AFP discontinuation was due to adverse events, drug interactions, insurance coverage, and other reasons in 101/147 (68.7%), 27 (18.4%), 13 (8.8%), and 6 (4.1%) patients, respectively. Early-voriconazole-AFP discontinuation occurred in 73/327 (22.3%) patients due to hepatotoxicity. Important predictors for early-voriconazole-AFP discontinuation included: graft-versus-host disease grade ≥2 (odds ratio [OR]: 1.9, *P*-value: .02), alanine-aminotransferase ≥75 IU/ml on voriconazole-administration day-14 (OR: 5.6, *P*-value: .02) and total bilirubin ≥1.3 mg/dl on voriconazole-administration day-7 (OR: 3.0, *P*-value: .03). There were 13 proven/probable invasive fungal infections by day-180 post-HCT (8/147, 5.4%, and 5/180, 2.8% in the early-discontinuation and SOC-groups, respectively; log-rank:0.13). By day-180 post HCT, 23/147 (15.6%) and 14/180 (7.8%) patients in the early-discontinuation and SOC-groups had died, respectively (log-rank:0.03). Voriconazole-AFP was discontinued in up to 45% of allo-HCTr. Hepatotoxicity during the first 2 weeks post-HCT is a significant predictor of early-voriconazole-AFP discontinuation.

Key words: voriconazole, invasive fungal infections, allogeneic hematopoietic cell transplant.

Introduction

Primary antifungal prophylaxis (AFP) with fluconazole, micafungin, or voriconazole is recommended during the first 75 days after a hematopoietic cell transplant (HCT), while posaconazole is the preferred AFP in cases of severe graft-versus-host disease (GvHD).[1–4] However, the use of voriconazole as AFP in allogeneic HCT recipients may be hindered due to variable pharmacokinetics, interpersonal variability and drug-drug interactions.[5–8] In addition, voriconazole-associated adverse events (AEs), including neurotoxicity, visual abnormalities and, most importantly, liver function impairment are frequently encountered in allogeneic HCT recipients.[9–13] Moreover, we have

previously demonstrated that premature discontinuation of voriconazole AFP may occur during the early post-transplantation period and before the cessation of immunosuppression in up to one third of patients due to, predominately, liver toxicity.[14] The aim of this study was to describe the clinical experience of voriconazole as primary AFP in allogeneic HCT recipients in a cancer center. More specifically, we sought to describe the rates and risk factors for discontinuation of voriconazole AFP during the first 75 days after an allogeneic HCT.

Methods

Study design

This was a single-center retrospective observational study of all adult (≥18 years) allogeneic HCT recipients between 1 January 2014 and 31 December 2016 at Memorial Sloan Kettering Cancer Center (MSKCC), who received a minimum of two doses of voriconazole as primary AFP post-HCT with available liver function tests at baseline and during voriconazole administration. Patients who did not receive voriconazole due to allergy, previous AEs or other reasons, or had a proven/probable invasive fungal infection (IFI) within 60 days prior to their HCT, were excluded. The study was approved by the MSKCC Institutional Review Board.

Antifungal prophylaxis strategy

Per institutional standard of care (SOC), an echinocandin (e.g., micafungin) was administered as primary AFP to all allogeneic HCT recipients starting 2 days (day -2) before until day +7 post-HCT or steady state levels of calcineurin inhibitors, when AFP was switched to voriconazole.[7] Voriconazole was continued until at least day +75 after HCT or cessation of immunosuppression. Of note, voriconazole therapeutic drug monitoring was not routinely performed at our institution during the study period.

Data collection

Demographics, underlying hematologic malignancy, type of transplant (unmodified vs T-cell depleted vs umbilical cord), stem cell source (bone marrow [BM] vs peripheral blood stem cells [PBSC] vs cord blood), donor-recipient matching, and conditioning regimen were recorded. Incidence of probable or proven IFI from day 0 until day +180 from HCT and voriconazole administration details (voriconazole initiation day, duration of AFP, mode of administration, loading and maintenance dose, AEs, and reasons of voriconazole discontinuation) were recorded. Liver function tests were recorded, including alanine transaminase (ALT), alkaline phosphatase and total bilirubin, before the start of voriconazole (baseline), during the period of voriconazole AFP, and 2 and 4 weeks after the end of voriconazole administration were recorded. All-cause mortality was also recorded.

Definitions

IFIs were defined based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus guidelines.[15] *Ex vivo* T-cell depletion was accomplished by positive selection of $CD34^+$ stem cells by using a CliniMACS CD34 Reagent system.[16] Acute graft-versus-host disease (GvHD) ≥ grade 2 was defined based on established guidelines.[17]

Statistical analysis

Categorical variables were compared by the chi-square test while continuous variables were compared by a t-test. Risk factors for voriconazole discontinuation (i) at any time, (ii) by day +14 and (iii) by day +28 post-HCT were identified using logistic regression models. The following independent variables were evaluated in univariable analyses: demographics, underlying disease, HCT characteristics, GvHD prophylaxis, GvHD grade ≥2, cytomegalovirus (CMV) serostatus, voriconazole administration variables, and ALT and total bilirubin at baseline and by days 7, 14, and 28 post-voriconazole administration. Variables with a *P*-value <.10 in univariable analyses were subsequently introduced into multivariable logistic regression models in a stepwise fashion. *P*-values of <.05 were considered significant. All analyses were performed by Stata 12.

Results

Patient population

A total of 435 patients received an allogeneic HCT during the study period, of which 108 patients were excluded due to previous AEs with voriconazole (9/108, 8.3%), baseline liver impairment precluding voriconazole use (41/108, 38%), proven or probable IFI within 60 days prior to HCT (13, 12%) or after HCT before the intended date of voriconazole initiation (4, 3.7%), recommendation to use antifungal agents other than voriconazole by the infectious disease service (8, 7.4%), fear of voriconazole toxicity (5, 4.6%), potential drug-drug interaction (3, 2.8%), death before the intended date of voriconazole initiation (3, 2.8%), and other reasons (22, 20.4%).

A total of 327 patients were included in this study (Table 1). The median age was 55 years, and almost 80% of the patients were white. The most common underlying disease prior to HCT was acute myeloid leukemia (112/327, 34.3%), followed by lymphoma (66, 20.2%) and myelodysplastic syndrome (47, 14.4%). A total of 143 (43.7%) HCT were from a matched unrelated donor, while haploidentical HCT accounted for 18 (5.5%) patients. The majority (176, 53.8%) of patients received a reduced intensity conditioning regimen, while others received a myeloablative conditioning regimen (135, 41.3%).

Table 1. Baseline patient characteristics.

Patient characteristic	Total number of patients N: 327 (%)
Demographics	
Age, median years (IQR)	55 (42.7–64.5)
Sex, female	145 (44.3)
Ethnicity	
White	259 (79.2)
Black	27 (8.3)
Asian	15 (4.6)
Other/Unknown	26 (7.9)
Underlying disease	
Acute myeloid leukemia	112 (34.3)
Acute lymphocytic leukemia	39 (11.9)
Myelodysplastic syndrome	47 (14.4)
Multiple myeloma	30 (9.2)
Lymphoma	66 (20.2)
Other[α]	33 (10)
HCT characteristics	
Donor type	
Matched related	82 (25.1)
Matched unrelated	143 (43.7)
Mismatched unrelated	84 (25.7)
Haploidentical	18 (5.5)
HCT source	
Bone marrow	33 (10.1)
Peripheral blood stem cells	242 (74.0)
Cord blood	31 (9.5)
Cord blood / peripheral blood stem cells	21 (6.4)
HCT manipulation	
Ex vivo T-cell depletion (CD34 + selected)	110 (33.6)
Conditioning	
Myeloablative	135 (41.3)
Reduced intensity	176 (53.8)
Nonablative	16 (4.9)
GvHD prophylaxis	
Tacrolimus + methotrexate[β]	120 (36.7)
Cyclosporine + mycophenolate mofetil	52 (15.9)
Tacrolimus + mycophenolate mofetil[γ]	28 (8.6)
Tacrolimus + sethotrexate + sirolimus	12 (3.7)
Others[δ]	5 (1.5)
Ex vivo T-cell depletion (CD34 + selected)	110 (33.6)
CMV serostatus	
D+/R+	105 (32.1)
D+/R−	39 (11.9)
D−/R+	79 (24.2)
D−/R−	104 (31.8)

D, donor; CMV, cytomegalovirus; GvHD, graft versus host disease; HCT, hematopoietic cell transplant; IFI, invasive fungal infection; R: recipient.
[α] Other underlying disease included: chronic leukemia (N: 16), myeloproliferative syndrome (N: 11), aplastic anemia (N: 2) and nonmalignant hematologic disorder (N: 4).
[β] In addition to tacrolimus + methotrexate, nine patients also received bortezomib, six patients also received maraviroc.
[γ] In addition to tacrolimus + mycophenolate mofeti, three patients also received methotrexate, 22 patients also received cyclophosphamide.
[δ] Included three cyclophosphamide, one cyclophosphamide/mycophenolate mofetil/sirolimus, and one cyclophosphamide/sirolimus.

Table 2. Voriconazole administration characteristics.

Voriconazole characteristics	Total number of patients N: 327 (%)
Time of voriconazole administration	
Initiation, median days post-HCT (mean; range)	7 (8.6 ; 1, 43)
Total days of voriconazole administration, median (mean; range)	69 (57.9 ; 1, 100)
Voriconazole dosing	
Loading dose given	292 (89.3)
Maintenance dose	
200 mg twice daily	48 (14.7)
4 mg/kg twice daily	279 (85.3)
Voriconazole mode of administration	
Loading dose, IV	270 (82.6)
Voriconazole administration, day 1–3[α]	
IV (only)	237 (73.4)
PO (only)	51 (15.8)
IV/PO (administration changed from IV to PO or vice-versa)	35 (10.8)
Voriconazole administration, day 1–7[β]	
IV (only)	95 (31.8)
PO (only)	48 (16.0)
IV/PO (administration changed from IV to PO or vice versa)	156 (52.2)
Voriconazole administration, day 1–14[γ]	
IV (only)	37 (13.2)
PO (only)	42 (15)
IV/PO (administration changed from IV to PO or vice versa)	202 (71.8)

HCT, hematopoietic cell transplant, IV, intravenous, PO, oral; SD, standard deviation.
[α] Data were available for 323 patients overall.
[β] Data were available for 299 patients overall.
[γ] Data were available for 281 patients overall.

Voriconazole administration data

Voriconazole was started at a median of 7 days (mean: 8.6; range 1, 43) post-HCT and continued for a median of 69 days (mean: 57.9; range 1, 100) (Table 2). A loading dose was administered in 292 (89.3%) patients (administered intravenously in 270/292 patients, 92.5%) and maintenance dose was weight-based in 279 (85.3%) patients. Mode of administration varied in the cohort, with most patients treated with intravenous (IV) voriconazole during the first 3 days of administration, with transition to oral (PO) after the first week of treatment. A total of 180 (55%) patients continued voriconazole prophylaxis as per institutional SOC (SOC group) for a median of 90 days (mean: 84; range 2, 100). In 147 (45%) patients, voriconazole prophylaxis was discontinued prematurely (early-discontinuation group) at a median of 20 days (mean: 25.6; range 1, 89; *t*-test *P*-value <.001) (Fig. 1A). Among the 147 patients in the early-discontinuation group, 137 (93.2%) patients were started on another antifungal agent for primary antifungal prophylaxis: 65/137 (47.4%)

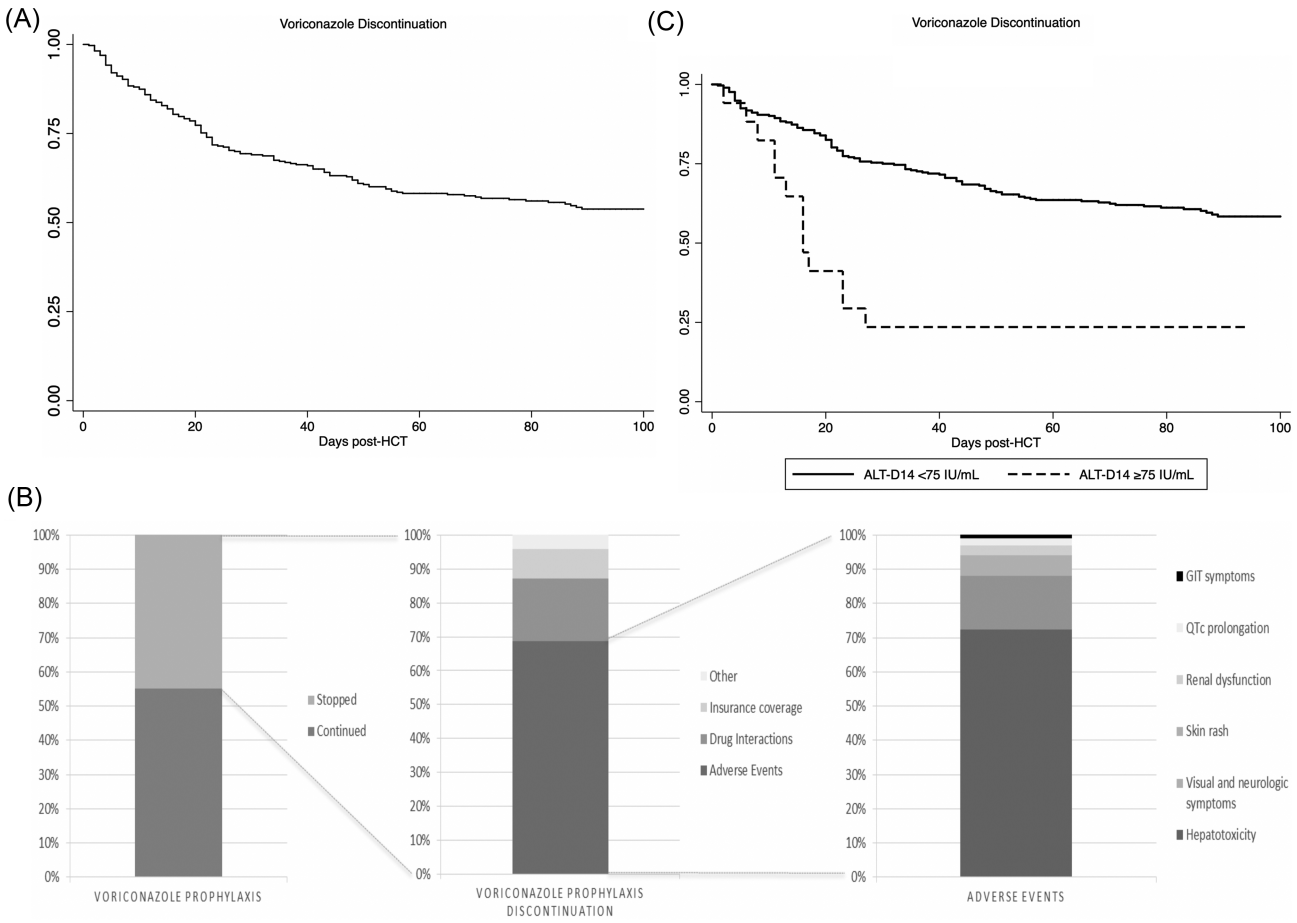


Figure 1. (A) Rate of voriconazole discontinuation in a cohort of allogeneic hematopoietic cell transplant (HCT) recipients. (B) Presentation of proportions of patients with discontinuation of voriconazole prophylaxis and the reasons for discontinuation. (C) Rate of voriconazole discontinuation based on the alanine aminotransferase (ALT) level by post-HCT day 14.

on posaconazole, 54 (39.4%) on micafungin, 14 (10.2%) on fluconazole, 3 (2.2%) on isavuconazole, and 1 (0.8%) patient on liposomal amphotericin B. In 10/147 (6.8%) patients no additional antifungal prophylaxis was administered after discontinuation of voriconazole. Voriconazole was resumed in 27/147 (18.4%) of patients. Voriconazole trough blood levels were measured in only 34 (10.4%) patients once during the first 10 days of voriconazole administration. Voriconazole trough level was at a mean of 2.2 mg/l (range: 0.3, 7.8): 2.1 mg/l (range: 0.3, 4.9) in 19 and 2.3 mg/l (range: 0.3, 7.8) in 15 patients in the SOC and early-discontinuation groups, respectively (*P*-value: .65).

Voriconazole discontinuation

Among the 147 patients in the early-discontinuation group, voriconazole was prematurely discontinued in 101 (68.7%) patients due to AEs, followed by drug-drug interactions in 27 (18.4%) patients and other reasons in six (4.1%) patients: three patients had suboptimal serum voriconazole levels, two patients were changed to empirical antifungal agent treatment, and one patient could not receive voriconazole for other reasons (Fig. 1B). In 13 (8.8%) patients, voriconazole was discontinued due to insurance coverage issues. Among the 101 patients with premature voriconazole prophylaxis discontinuation due to AEs, liver function test abnormalities were the most frequent AE observed in 73/101 (72.3%) patients, followed by visual hallucinations and central nervous system symptoms (16, 15.8%), skin rash (6, 5.9%), renal dysfunction (3, 3%) and other (3, 3%: 2 patients for QTc prolongation and one patient with gastrointestinal symptoms).

Liver function tests

Overall, voriconazole was discontinued in 73 of 327 (22.3%) patients due to liver function abnormalities. Patients with abnormal liver function tests were more likely to have stage ≥2 liver GvHD (4/73, 5.5%) when compared to the remaining 254 patients in this cohort, amongst whom none developed liver GvHD (*P*-value >.002). At the time of voriconazole discontinuation, ALT and AST were ≥100 IU/ml in 39 (12.1%) and 27 (8.4%) of 321 patients with available values, respectively. The mean ALT at voriconazole initiation was similar between the

two groups: 36.7 IU/ml (standard deviation [SD]: 122) in the early-discontinuation and 24.8IU/ml (SD: 16) for the SOC patient group (*P*-value = .2; Fig. 2B). However, the mean ALT at the end of voriconazole administration was significantly higher in the early-discontinuation (76.9 IU/ml, SD: 167.9) than the SOC-patient group (38.6 IU/ml, SD: 130; *P*-value: .02). Similar observations were made for total bilirubin (Fig. 2B). Within 7 days after voriconazole discontinuation, the mean ALT was similar between the two groups (early-discontinuation: 44.9 IU/ml vs SOC: 35.6 IU/ml, *P*-value = .30). However, the mean total bilirubin remained significantly higher in the early-discontinuation (1.1 mg/dl, SD: 2.4) compared to the SOC group (0.46 mg/dl, SD: 0.5; *P*-value = .002) by 7 days post-voriconazole discontinuation.

Risk factors for voriconazole discontinuation

Three different analyses were performed to identify predictors of voriconazole discontinuation: (a) at any time, (b) by day 14 post-HCT, and (c) by day 28 post-HCT (Supplement Tables 1 and 2; Supplement Fig. 1). Important predictors for early voriconazole discontinuation at any time in multivariable analyses included: GvHD ≥2 grade (odds ratio [OR]: 1.9, *P*-value: .02), ALT on day 14 of voriconazole administration ≥75 IU/ml (OR: 5.6, *P*-value: .02) and total bilirubin on day 7 of voriconazole administration ≥1.3 mg/dl (OR: 3.0, *P*-value: .03) (Fig. 1C). Risk factors for discontinuation of voriconazole by day 14 post-HCT in multivariable analyses included: age ≥65 years (OR: 3.2, *P*-value: .001) and baseline ALT ≥75 IU/ml (OR: 5.4, *P*-value: .04). Elevated ALT by day 14 of voriconazole administration ≥75 IU/dl was the only significant risk factor for discontinuation of voriconazole by day 28 post-HCT in multivariable analyses (OR: 7.7, *P*-value: .01).

Clinical outcomes

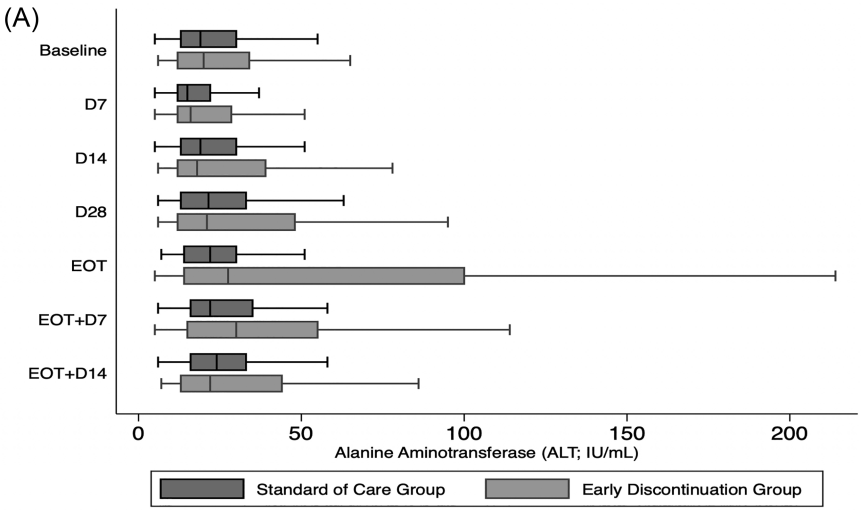
There were 13 proven and probable IFI observed during the first 180 days in this cohort: 8/147 (5.4%) and 5/180 (2.8%) in the early-discontinuation and the SOC-group, respectively (log-rank: 0.13; Fig. 3A). In the SOC group, there was one breakthrough probable invasive mould infection (IMI) during prophylaxis with voriconazole, while three additional IMI and one case of coccidiomycosis occurred after discontinuation of primary voriconazole prophylaxis. In the early-discontinuation group, there were four breakthrough IFI during voriconazole administration (two cases of invasive candidiasis, one infection due to *Saccharomyces* spp., and one probable IMI), while four cases of probable IMI occurred after discontinuation of voriconazole administration. By day-180 post-HCT, 23 (15.6%) of 147 patients in the early-discontinuation and 14 (7.8%) of 180 patients in the SOC patient groups had died (log-rank: 0.03; Fig. 3B). In mortality predictor analysis, only age (OR: 1.03, *P*-value: .04) and early voriconazole discontinuation (OR: 2.3, *P*-value: .02) were significant predictors of mortality by day-180 post-allogeneic HCT (Supplement Table 3).

Discussion

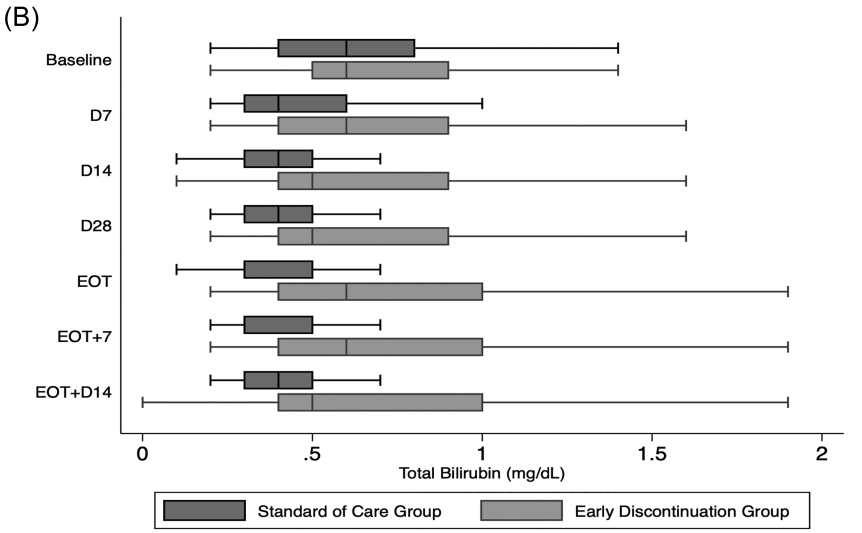
In this retrospective single-center study we report a high discontinuation rate of primary AFP with voriconazole in up to 45% of allogeneic HCT recipients within the first 3 months post-transplant. In almost one in five patients, voriconazole AFP was discontinued due to hepatotoxicity, with liver test abnormalities during the first 2 weeks of voriconazole AFP administration predicting early voriconazole discontinuation. There was a trend for lower rates of proven and probable IFI and a survival benefit in patients who continued to receive AFP as per institutional SOC.

Almost half of the patients had to stop voriconazole in this series. This rate of voriconazole discontinuation is higher than previously reported, and highlights the difficulties associated with the administration of this agent in clinical practice.[18] Voriconazole-associated AEs and drug-drug interactions were the main reasons leading to drug discontinuation. In addition to liver function test abnormalities, visual hallucinations, other neurological symptoms, renal dysfunction, and prolonged QTc were among the most commonly observed AEs. It is likely that in a proportion of patients, voriconazole-associated AEs could have been due to elevated voriconazole blood levels. Voriconazole therapeutic drug monitoring (TDM) has been associated with a significant reduction in voriconazole-associated AEs and discontinuation rates.[18] Lack of routine TDM in this series could have, in part, contributed to more frequent toxic levels and therefore higher rates of discontinuation.

Liver function abnormalities are common in allogeneic HCT recipients due to a large variety of potential causes, including, but not limited to, viral and other infections, GvHD, veno-occlusive disease, and concomitant drug administration, including azoles. Voriconazole-associated liver toxicity has been described in up to 16% of patient in the setting of prospective randomized clinical trials.[9,11,19,20] Our observations are consistent with those prior reports, with only 8–12% of patients in this series having elevated transaminases at ≥100 IU/ml at the time of voriconazole discontinuation. In fact, liver function test abnormalities in this series were rather modest, with the mean ALT value at the end of voriconazole administration being only twice the ALT upper limit of normal in the early-discontinuation group. Despite this moderate degree of hepatotoxicity, voriconazole was discontinued in almost one in five patients due to liver test abnormalities. This is consistent with prior observations at our institution.[14] In fact, moderate elevations in ALT (≥75 IU/ml) and/or total bilirubin (≥1.3 mg/dl) during the first 2 weeks of voriconazole AFP administration were significant predictors of early discontinuation of voriconazole. The above suggests that, although a causal relationship between voriconazole and hepatotoxicity cannot always



	Standard of Care Group		Early Discontinuation Group		P-value
	Mean (IU/ml)	Standard Deviation	Mean (IU/ml)	Standard Deviation	
ALT baseline	24.8	16.4	35	117	0.12
ALT Day 7	20.1	17.2	24.6	28.7	0.04
ALT Day 14	24.8	19.6	32.6	37.4	0.008
ALT Day 28	24.6	14.6	33.7	31	0.002
ALT EOT	38.5	130	71.6	161	0.02
ALT EOT + D7	35.6	91.6	43.6	40.8	0.18
ALT EOT + D14	28.9	20.5	36.5	33	0.008



	Standard of Care Group		Early Discontinuation Group		P-value
	Mean (mg/dL)	Standard Deviation	Mean (mg/dL)	Standard Deviation	
TBil baseline	0.64	0.3	0.69	0.34	0.06
TBil Day 7	0.51	0.33	0.61	0.44	<0.001
TBil Day 14	0.48	0.31	0.81	1.2	<0.001
TBil Day 28	0.43	0.26	0.6	0.4	<0.001
TBil EOT	0.44	0.46	0.85	0.95	<0.001
TBil EOT + D7	0.46	0.48	1.0	2.3	0.002
TBil EOT + D14	0.48	0.47	1.12	3.0	0.004

Figure 2. (A) Boxplots of alanine aminotransferase (ALT) between patients who continued to receive voriconazole prophylaxis as per standard of care ("standard of care group") and those patients who discontinued voriconazole prophylaxis due to variable reasons ("early discontinuation group") at different time-points post-voriconazole prophylaxis initiation. (B) Boxplots of total bilirubin (TBil) between patients who continued to receive voriconazole prophylaxis as per standard of care ("standard of care group") and those patients who discontinued voriconazole prophylaxis due to variable reasons ("early discontinuation group") at different time-points post-voriconazole prophylaxis initiation. D, day; EOT, end of treatment; ALT, alanine aminotransferase; TBil, total bilirubin.

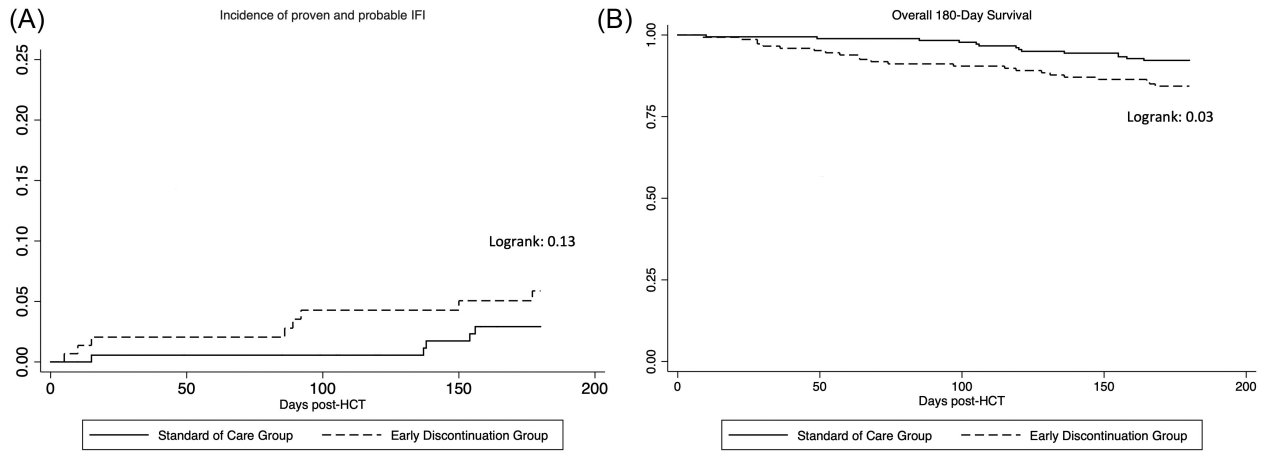


Figure 3. (A) Incidence of invasive fungal infections between allogeneic hematopoietic cell transplant recipients whose voriconazole prophylaxis was continued as per standard of care ("standard of care group") and those patients who discontinued voriconazole prophylaxis due to variable reasons ("early discontinuation group"). (B) Overall 180-day mortality between allogeneic hematopoietic cell transplant recipients whose voriconazole prophylaxis was continued as per standard of care ("standard of care group") and those patients who discontinued voriconazole prophylaxis due to various reasons ("early discontinuation group").

be definitively demonstrated, even mild liver test abnormalities may lead clinicians to stop the administration of this agent in up to 20–25% of patients due to fear or suspicion that voriconazole may be contributing to the observed test abnormalities.

The overall effect of voriconazole discontinuation on allogeneic HCT recipients is not well described. We observed a trend toward more IFI in patients who had to discontinue voriconazole AFP. This retrospective study was not powered to detect the effect of voriconazole AFP on the incidence of IFI. However, the incidence of IFI in the SOC and early discontinuation groups, respectively, was similar to that reported in a clinical trial that compared voriconazole to fluconazole as primary AFP in allogeneic HCT recipients.[10] Early voriconazole discontinuation was associated with higher all-cause mortality by day 180 post-transplant. It is not possible to assess the direct effect of voriconazole discontinuation on mortality, and it is possible that voriconazole was more likely to be stopped in patients with more comorbidities and worse overall prognosis. However, these data taken together suggest that patients in whom clinicians are more likely to discontinue voriconazole AFP may be at higher risk for complications. These patients could potentially benefit from more intensive management and closer follow-up to optimize clinical outcomes.

This study has several limitations, including its retrospective nature and lack of data on voriconazole levels and concomitantly administered drugs. Attribution of hepatotoxicity to voriconazole or other potential causes was not feasible but reflects the real life limitations of clinical practice in allogeneic HCT recipients early post-transplant.

In conclusion, this study describes the clinical experience with voriconazole AFP among unselected allogeneic HCT recipients in a single cancer center. Adherence to voriconazole AFP among HCT recipients is challenging with early discontinuation observed in a substantial proportion of HCT recipients, mostly due to anticipated AEs. Moderate abnormalities in liver function tests during the first 2 weeks of administration may predict early voriconazole discontinuation. Strategies for monitoring toxicities and managing intolerance of voriconazole are essential for HCT recipients receiving voriconazole as AFP.

Supplementary material

Supplementary data are available at *MMYCOL* online.

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Conflicts of interest

M.P. reports honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Cidara Therapeutics, Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee. D.N. has received research support from MSD and has served as has received consulting fees from Roche Diagnostics, MSD, Pfizer, Basilea, and Gilead. G.A.P. has been an investigator for Shire, Merck, Chimerix, and Astellas, and has received consulting fees from Shire, Merck, Chimerix, and Astellas. All other authors report no conflicts of interest.

References

1. 2.2016 NGV. Prevention and treatment of Cancer-Related Infections. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)* 2016; https://oralcancerfoundation.org/wp-content/uploads/2016/09/infections.pdf. Accessed 5 February, 2020.
2. Freifeld AG, Bow EJ, Sepkowitz KA et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011; 52: e56–93.
3. Taplitz RA, Kennedy EB, Bow EJ et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol*. 2018: JCO1800374.
4. Tomblyn M, Chiller T, Einsele H et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009; 15: 1143–1238.
5. Kim SH, Kwon JC, Park C et al. Therapeutic drug monitoring and safety of intravenous voriconazole formulated with sulfobutylether beta-cyclodextrin in haematological patients with renal impairment. *Mycoses*. 2016; 59: 644–651.
6. Kim SH, Yim DS, Choi SM et al. Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients. *Int J Infect Dis*. 2011; 15: e753–758.
7. Rosillo C, Avila AM, Huang YT et al. Sequential systematic anti-mold prophylaxis with micafungin and voriconazole results in very low incidence of invasive mold infections in patients undergoing allogeneic hematopoietic stem cell transplantation. *Transplant Infect Dis*. 2018; 20: e12897.
8. Ceberio I, Dai K, Devlin SM et al. Safety of voriconazole and sirolimus coadministration after allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2015; 50: 438–443.
9. Maertens JA, Raad II, Marr KA et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet*. 2016; 387: 760–769.
10. Wingard JR, Carter SL, Walsh TJ et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010; 116: 5111–5118.
11. Marr KA, Schlamm HT, Herbrecht R et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med*. 2015; 162: 81–89.
12. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother*. 2012; 56: 4793–4799.
13. Hoy Z, Dodds Ashley ES, Weinberg GA, Krysan DJ. Voriconazole Therapeutic Drug Monitoring. *J Pediatric Infect Dis Soc*. 2014; 3: 270–271.
14. Amigues I, Cohen N, Chung D et al. Hepatic safety of voriconazole after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2010; 16: 46–52.
15. De Pauw B, Walsh TJ, Donnelly JP et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008; 46: 1813–1821.
16. Cho C, Perales MA. Expanding therapeutic opportunities for hematopoietic stem cell transplantation: T cell depletion as a model for the targeted allograft. *Annu Rev Med*. 2019; 70: 381–393.
17. Przepiorka D, Weisdorf D, Martin P et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995; 15: 825–828.
18. Park WB, Kim NH, Kim KH et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis*. 2012; 55: 1080–1087.
19. Herbrecht R, Denning DW, Patterson TF et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002; 347: 408–415.
20. Walsh TJ, Pappas P, Winston DJ et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med*. 2002; 346: 225–234.

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

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Summary

Background Isavuconazole is a novel triazole with broad-spectrum antifungal activity. The SECURE trial assessed efficacy and safety of isavuconazole versus voriconazole in patients with invasive mould disease.

Methods This was a phase 3, double-blind, global multicentre, comparative-group study. Patients with suspected invasive mould disease were randomised in a 1:1 ratio using an interactive voice–web response system, stratified by geographical region, allogeneic haemopoietic stem cell transplantation, and active malignant disease at baseline, to receive isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) or voriconazole (6 mg/kg intravenously twice daily on day 1, 4 mg/kg intravenously twice daily on day 2, then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onwards). We tested non-inferiority of the primary efficacy endpoint of all-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug (intention-to-treat [ITT] population) using a 10% non-inferiority margin. Safety was assessed in patients who received the first dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00412893.

Findings 527 adult patients were randomly assigned (258 received study medication per group) between March 7, 2007, and March 28, 2013. All-cause mortality from first dose of study drug to day 42 for the ITT population was 19% with isavuconazole (48 patients) and 20% with voriconazole (52 patients), with an adjusted treatment difference of –1·0% (95% CI –7·8 to 5·7). Because the upper bound of the 95% CI (5·7%) did not exceed 10%, non-inferiority was shown. Most patients (247 [96%] receiving isavuconazole and 255 [98%] receiving voriconazole) had treatment-emergent adverse events (p=0·122); the most common were gastrointestinal disorders (174 [68%] *vs* 180 [69%]) and infections and infestations (152 [59%] *vs* 158 [61%]). Proportions of patients with treatment-emergent adverse events by system organ class were similar overall. However, isavuconazole-treated patients had a lower frequency of hepatobiliary disorders (23 [9%] *vs* 42 [16%]; p=0·016), eye disorders (39 [15%] *vs* 69 [27%]; p=0·002), and skin or subcutaneous tissue disorders (86 [33%] *vs* 110 [42%]; p=0·037). Drug-related adverse events were reported in 109 (42%) patients receiving isavuconazole and 155 (60%) receiving voriconazole (p<0·001).

Interpretation Isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive mould disease. Isavuconazole was well tolerated compared with voriconazole, with fewer study-drug-related adverse events. Our results support the use of isavuconazole for the primary treatment of patients with invasive mould disease.

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Introduction

Invasive mould disease represents a challenge, especially in patients with haematological malignant disease and haemopoietic stem cell transplantation, solid organ transplant recipients, and patients in intensive-care units.[1] Invasive mould disease still accounts for substantial mortality in these patients.[1,2]

The available range of antifungal drugs that are active against mould disease has shortcomings. Polyenes, once the mainstay of anti-mould therapy, now have a limited role because of toxicity concerns and the requirement for intravenous administration.[3] Echinocandins have an excellent safety profile; however, there is relatively little experience in their use for the primary treatment of invasive mould disease.[4,5] Posaconazole is licensed for the salvage treatment of invasive mould disease,[6] but data to support its first-line use are lacking. Voriconazole has been endorsed by international guidelines as primary treatment for invasive aspergillosis,[2,7,8] as well as some other mould infections.[9] However, drug interactions, pharmacokinetic variability, short-term acute toxicities (including photopsia, visual

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Research in context

Evidence before this study

We searched PubMed without time or language limitation with the search criteria ("invasive"[All Fields] AND ("aspergillosis"[MeSH Terms] OR "aspergillosis"[All Fields])) AND (("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) AND (("registries"[MeSH Terms] OR "registries"[All Fields] OR "trial"[All Fields])), up to October, 2015. 55 references were found, of which 36 were categorised as clinical trials. By excluding prevention trials and studies in patients with *Candida* infections only, 15 clinical trials or cohorts or registries were identified, with nine studies before 2003. Mortality in all trials was similarly high. Only one study was well powered, prospective, and randomised-controlled prior to the beginning of the trial. Overall 10 studies were non-randomised or uncontrolled in nature; four studies were identified in patients refractory or intolerant to therapy; three trials included only patients with non-haematological disease (mainly solid organ transplant recipients). The only study published before 2003 was that by Herbrecht and colleagues (2002), which showed significantly improved outcomes, including survival advantage of voriconazole compared with conventional amphotericin B.

Added value of this study

SECURE is a prospective, double-blind, randomised, global trial demonstrating that the novel triazole isavuconazole is non-inferior to voriconazole for the primary treatment of invasive aspergillosis and disease caused by other moulds. Additionally, isavuconazole was well tolerated compared with voriconazole, with significantly fewer study drug-related adverse events and adverse events of the skin, eye, and hepatobiliary systems.

Implications of all the available evidence

Voriconazole is the current gold standard for treatment of invasive aspergillosis but is limited by drug–drug interactions and safety concerns. Moreover, many non-*Aspergillus* moulds, such as the agents of mucormycosis, are often resistant to voriconazole. This trial offers strong evidence that isavuconazole is an appropriate alternative to voriconazole for the primary treatment of invasive aspergillosis and other mould disease.

hallucinations, and abnormalities in liver function), long-term toxicities (such as skin carcinogenesis and fluorosis), concerns about β-cyclodextrin administration in the setting of impaired renal function, and recommendations for therapeutic drug monitoring have been problematic for patients.[10]

The water-soluble prodrug isavuconazonium sulfate was developed to facilitate intravenous administration without the need for potentially nephrotoxic excipients such as β-cyclodextrin. Isavuconazole, the active moiety, displays excellent bioavailability (roughly 98%)[11] after oral administration without any clinically relevant food effects. Isavuconazole is a broad-spectrum triazole that has demonstrated potent activity in animal models of invasive aspergillosis,[12] mucormycosis,[13] invasive candidiasis,[14] and cryptococcosis.[15] Isavuconazonium sulfate was approved in 2015 by the US Food and Drug Administration (FDA) for the treatment of invasive aspergillosis and invasive mucormycosis,[16] and by the European Medicines Agency for the treatment of invasive aspergillosis and of mucormycosis when amphotericin B is inappropriate.[17]

We conducted a phase 3, double-blind trial to compare the efficacy and safety of intravenous and oral formulations of isavuconazole to voriconazole for the primary treatment of invasive mould disease caused by *Aspergillus* spp or other filamentous fungi (the SECURE trial).

Methods

Study design and participants

This was a phase 3, randomised, double-blind, international, multicentre, non-inferiority study of isavuconazole versus voriconazole for the primary treatment of invasive mould disease, conducted from 2007 to 2013. Enrolment was suspended from January, 2009, to March, 2011, to allow for completion of non-clinical toxicity studies and licensing activities.

Patients 18 years or older were eligible if they were considered to have invasive mould disease by meeting the criteria for proven, probable, or possible invasive mould disease caused by *Aspergillus* spp or other filamentous fungi.[18] Key exclusion criteria were hepatic dysfunction (bilirubin ≥3×upper limit of normal [ULN], alanine transaminase or aspartate transaminase ≥5×ULN, cirrhosis or chronic hepatic failure), or moderate to severe renal dysfunction (calculated creatinine clearance <50 mL/min). Mycological criteria for diagnosis of invasive mould disease included detection by cytology or direct microscopy of fungal elements indicating a mould, or by culture. A positive serum galactomannan test (single optical density index value ≥0·7 or two consecutive values ≥0·5) was regarded as mycological evidence for aspergillosis, except in patients receiving concomitant amoxicillin-clavulanate, piperacillin-tazobactam, or gluconate-containing plasma expanders. Galactomannan detection in broncho-alveolar lavage fluid was not accepted as a mycological criterion for probable aspergillosis because the galactomannan assay in fluid had not yet been approved by the US FDA. After the protocol was drafted, but before unblinding of the locked database, the FDA provided revised galactomannan criteria for probable disease. Subsequently, a prespecified analysis was performed using these criteria (appendix).[19] Full inclusion and exclusion criteria are detailed in the appendix.

Independent ethics committees or institutional review boards at participating sites approved the protocol and all

amendments. The study was conducted in accordance with the Declaration of Helsinki (2000) and the International Conference on Harmonisation Guidelines for Good Clinical Practice. For all sites, approval of the protocol was obtained from the governmental authorities. Written informed consent was obtained from patients or their legally authorised representatives before initiation of any trial procedures.

Randomisation and masking

Patients were centrally randomised using a third-party interactive response computer system to assign them to receive isavuconazole or voriconazole in a 1:1 allocation. Randomisation was performed using a block size of four and was stratified by geographical region, allogeneic haemopoietic stem cell transplantation, and active malignancy at study entry. All trial site personnel involved in patient care and non-site personnel were blinded to treatment assignment, except pharmacy personnel responsible for medication preparation. Placebo was used to maintain blinding by matching the frequency of daily dosing. Blinding codes and randomisation lists were prepared by the study funder's designee.

Procedures

Patients assigned to isavuconazole received isavuconazonium sulfate 372 mg (equivalent to isavuconazole 200 mg) intravenously three times a day on days 1 and 2, followed by either intravenous or oral isavuconazole 200 mg once daily, followed in 12 h by a corresponding placebo (excipient only) from day 3 onwards. Patients allocated to voriconazole received the labelled dose: 6 mg/kg intravenously twice daily on day 1, followed by 4 mg/kg intravenously twice daily on day 2. Voriconazole was given either intravenously (4 mg/kg twice daily) or orally (200 mg twice daily) from day 3 onwards. The protocol did not allow therapeutic drug monitoring (to maintain study blinding) and stipulated that the maximum treatment duration was to be 84 days.

Assessment of clinical symptoms and physical findings was conducted at screening and at all visits after day 3, including days 7, 14, 28, 42, 63, 84, end of treatment (if before day 84), and 4 weeks after end of treatment. Radiological and mycological assessments were performed between screening and day 7, on days 42 and 84, and at end of treatment. Additional radiological and mycological assessments were performed during treatment and follow-up if clinically indicated.

An independent data review committee, consisting of infectious disease experts who were masked to treatment allocation, was established to independently adjudicate the diagnosis of invasive mould disease at enrolment (including data up to day 7 as relevant). They also assessed clinical, mycological, radiological, and overall responses, at end of treatment, day 42, and day 84 (appendix). Consensus of three members of the data review committee per case was required for adjudication. A central radiologist, masked to treatment allocation, initially determined radiological responses at prespecified timepoints. Patients with radiological evidence at baseline but without post-baseline radiological follow-up were assumed not to have achieved treatment success.

Outcomes

The intention-to-treat (ITT) population, the primary efficacy population, included all patients who were enrolled, randomly assigned, and received at least one dose of medication. The modified intention-to-treat (mITT) population consisted of ITT patients with proven or probable invasive mould disease, as determined by the data review committee. The mycological intention-to-treat (myITT) population was a subset of the mITT population with proven or probable invasive aspergillosis (as assessed by the data review committee). The safety population included all enrolled patients who received their first dose of study drug, and is analysed by drug received (irrespective of study group assignment). We also assessed the primary outcome in a per-protocol population, excluding patients who met prespecified classification criteria (eg, met key exclusionary criteria, received at least three consecutive days of prohibited concomitant medications, or received less than 7 days of study drug). Additionally, we assessed the primary endpoint in a strictly defined intention-to-treat population (including all patients who were enrolled and randomly assigned, irrespective of whether they received any study drug) in a post-hoc analysis.

The primary efficacy endpoint was all-cause mortality from first dose of study drug to day 42 in the ITT population. The ITT population was chosen because it is representative of a population of patients requiring antifungal therapy in a real-world setting. Patients with unknown survival status were counted as deaths, defined by the date of last known follow-up; this approach was approved by the FDA. The key secondary endpoint was overall response (as assessed by the data review committee) at end of treatment in the mITT population (appendix). Other secondary endpoints included all-cause mortality from first dose of study drug to day 84, overall, clinical, mycological, and radiological responses (as assessed by the data review committee) on day 42, day 84, and end of treatment, as well as safety and tolerability.

Investigators evaluated safety and tolerability by monitoring adverse events and findings from physical examinations, vital signs, laboratory tests, electrocardiogram, and concomitant medication or surgery. Treatment-emergent adverse events were defined as an adverse event starting or worsening after first study drug administration until 28 days after the last dose. Study-drug-related adverse events included those reported as remotely, possibly, or probably related to the study drug by the blinded investigator.

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See Online for appendix

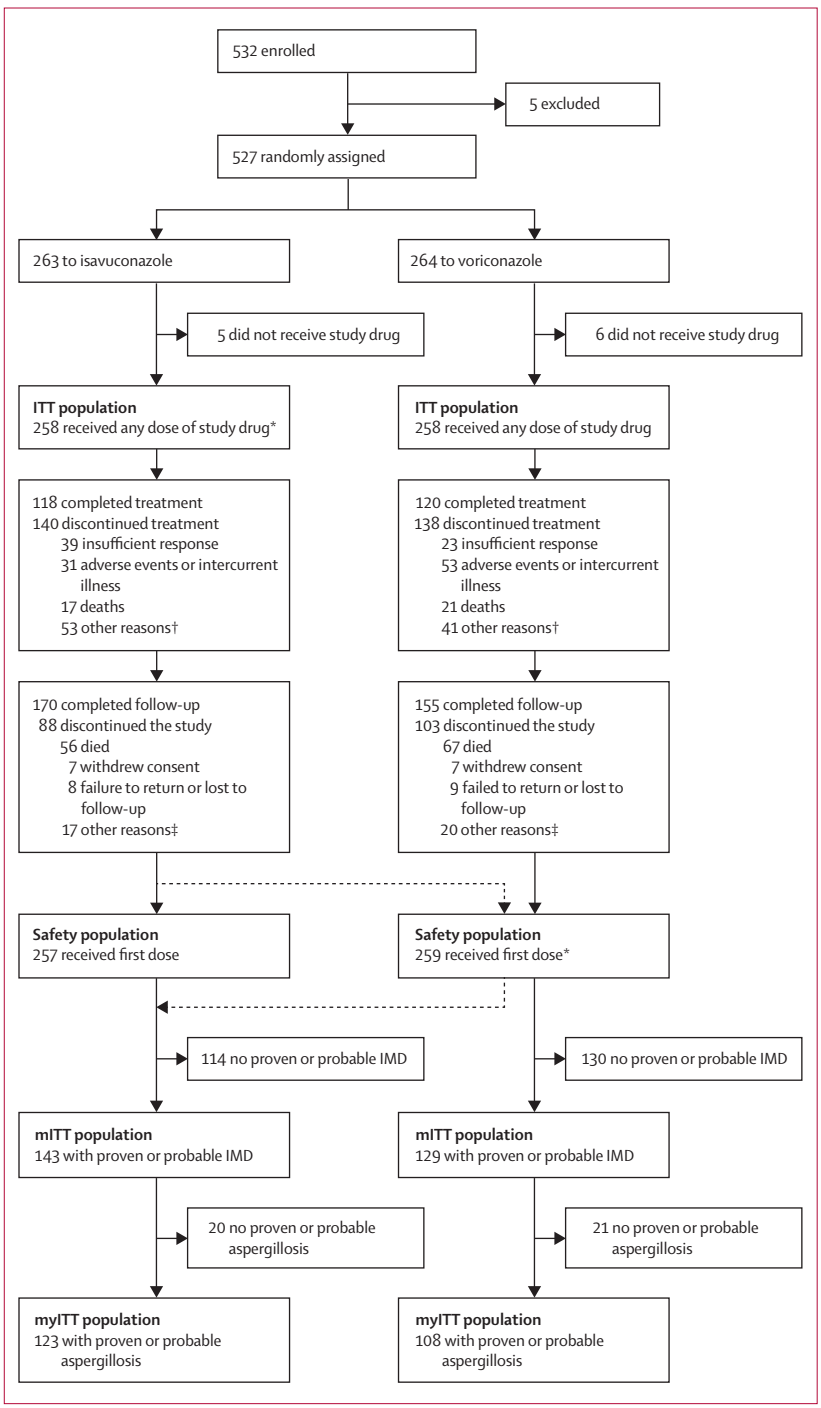

Figure 1: **Trial profile**
Enrolled refers to patients who provided written informed consent. IMD=invasive mould disease. ITT=intention to treat; all randomised patients who received study drug. mITT=modified intention to treat; ITT patients with proven or probable invasive mould disease. myITT=mycological intention to treat; mITT patients with proven or probable invasive aspergillosis. *Including one patient assigned to isavuconazole who received voriconazole for 7 days followed by isavuconazole oral study drug; this patient is included in the isavuconazole efficacy analysis and the voriconazole safety analysis. †Including failure to return or loss to follow-up, violation of selection at entry, other protocol deviation, did not cooperate, refused treatment, withdrew consent, and administrative or other. ‡Including adverse events or intercurrent illness and administrative or other.

Statistical analyses

Our sample size calculation was based on the primary efficacy endpoint, all-cause mortality in the ITT population from first dose of study drug to day 42. Roughly 255 patients per group were required for an 80% power to demonstrate that the upper limit of the 95% CI for a treatment difference was 10% or less (prespecified non-inferiority margin for this endpoint). This calculation was based on a one-sided, large-sample, normal-approximation and non-inferiority test at a 2·5% significance level. A 20% mortality rate was assumed for both drugs in the primary efficacy population.

To evaluate the efficacy (mortality endpoint) of amphotericin B over placebo in patients with invasive fungal disease caused by *Aspergillus* spp, the funder conducted a meta-analysis using historical individual patient data from 90 articles dating from 1952 to 2006. A 10% non-inferiority margin was established for the all-cause mortality rate from first dose of study drug to day 42 in untreated patients (ie, placebo) of 84·8% (95% CI 75·1 to 94·5). This estimation was further supported by a mortality rate of 100% in untreated patients reported by Denning.[20] The historical all-cause mortality rate from first dose of study drug to day 42 for voriconazole was 18·8% (95% CI 12·4 to 25·1), on the basis of a randomised comparative study assessing voriconazole and amphotericin B.[21] A conservative estimate of effect size for voriconazole compared with untreated (placebo) patients with invasive aspergillosis for all-cause mortality from first dose of study drug to day 42 was 50% (lower bound of placebo 95% CI minus upper bound of voriconazole 95% CI). Therefore, a 10% non-inferiority margin would provide statistical evidence that isavuconazole is superior to placebo, preserving more than 80% of the estimated voriconazole treatment effect. In a 2009 workshop on hospital-acquired and ventilator-associated pneumonia sponsored by the FDA, the Infectious Diseases Society of America, the American Thoracic Society, the Society of Critical Care Medicine, and the American College of Chest Physicians, it was proposed that a 10% non-inferiority margin for all-cause mortality in serious infections would be clinically acceptable.[22]

Adjusted treatment difference was calculated by a stratified Cochran-Mantel-Haenszel method with the randomisation strata of geographical region, allogeneic haemopoietic stem cell transplantation status, and active malignancy status. The 95% CI for the adjusted treatment difference was calculated on the basis of a normal approximation. Treatment-by-subgroup interaction (age, sex, race, ethnic origin, baseline neutropenic status, body-mass index, glomerular filtration rate, and enrolment period) was evaluated using a logistic regression according to the prespecified statistical significance value of $p<0·15$. For assessment of treatment-emergent adverse events, we did a prespecified comparison between the proportions of treatment-emergent adverse events reported in each system organ class between treatment groups, based on Fisher's exact

	Isavuconazole	Voriconazole
ITT population		
Number of patients	258	258
Age, years	51·1 (16·2)	51·2 (15·9)
Sex		
Men	145 (56%)	163 (63%)
Women	113 (44%)	95 (37%)
Geographical region		
North America	30 (12%)	28 (11%)
Western Europe, Australia, and New Zealand	105 (41%)	107 (41%)
Other*	123 (48%)	123 (48%)
Mean body-mass index, kg/m²	24·2	23·7
Risk factor		
Haematological malignancy	211 (82%)	222 (86%)
Allogeneic BMT/HSCT	54 (21%)	51 (20%)
Active malignancy at study entry	173 (67%)	187 (72%)
Absolute neutrophil count <500/mm³	163 (63%)	175 (68%)
Use of T-cell immunosuppressants	111 (43%)	109 (42%)
Use of corticosteroids	48 (19%)	39 (15%)
eGFR-MDRD		
<60 mL/min per 1·73 m²	20 (8%)	33 (13%)
≥60 mL/min per 1·73 m²	231 (92%)	217 (87%)
Missing	7	8
Primary underlying disease†		
Acute myeloid leukaemia	99 (38%)	126 (49%)
Acute lymphoblastic leukaemia	30 (12%)	24 (9%)
Lymphoma	33 (13%)	24 (9%)
Myelodysplastic syndrome	23 (9%)	14 (5%)
Chronic lymphocytic leukaemia	10 (4%)	13 (5%)
Aplastic anaemia	9 (3%)	7 (3%)
Chronic myeloid leukaemia	5 (2%)	8 (3%)
Multiple myeloma	5 (2%)	7 (3%)
Chronic obstructive pulmonary disease	5 (2%)	3 (1%)
Hodgkin's disease	2 (1%)	3 (1%)
Diabetes mellitus	4 (2%)	0
Certainty of diagnosis‡		
Proven invasive mould disease	29 (11%)	36 (14%)
Probable invasive mould disease	114 (44%)	93 (36%)
Possible invasive mould disease	88 (34%)	108 (42%)
No invasive mould disease	27 (10%)	21 (8%)
Mycological criteria		
No mycological evidence available§	92 (36%)	113 (44%)
Serum galactomannan positive	91 (35%)	94 (36%)
Non-sterile cytology, direct microscopy, or culture evidence of invasive mould disease	59 (23%)	39 (15%)
Sterile-site cytology, histopathology, or culture evidence of invasive mould disease	30 (12%)	34 (13%)
Autopsy	1 (<1%)	7 (3%)
mITT population		
Number of patients	143	129
Pathogen causing disease		
Aspergillus spp only	49 (34%)	39 (30%)
A fumigatus	32 (22%)	21 (16%)
A flavus	10 (7%)	12 (9%)
A niger	6 (4%)	2 (2%)
A terreus	4 (3%)	2 (2%)
A usti	0	1 (1%)
Aspergillus spp¶	1 (1%)	3 (2%)
A sydowi	1 (1%)	0
Aspergillus plus other filamentous fungi	3 (2%)	1 (1%)
A fumigatus	0	1 (1%)
A flavus	1 (1%)	0
A terreus	1 (1%)	0
Aspergillus spp¶	1 (1%)	0
Lichtheimia corymbifera	1 (1%)	0
Lichtheimia spp¶	1 (1%)	0
Scedosporium spp¶	1 (1%)	1 (1%)
Non-*Aspergillus* spp only	5 (3%)	6 (5%)
Rhizopus spp¶	1 (1%)	0
Mucor spp¶	0	1 (1%)
Fusarium solani	2 (1%)	0
Fusarium spp¶	1 (1%)	3 (2%)
Exserohilum rostratum	0	1 (1%)
Talaromyces marnefei	0	1 (1%)
Talaromyces spp¶	0	1 (1%)
Trichosporon inkin	1 (1%)	0
Filamentous fungi (no species identified)	14 (10%)	15 (12%)
Galactomannan positive only‖	72 (50%)	68 (53%)
Location of disease		
LRTD only	116 (81%)	107 (83%)
LRTD plus other organ	12 (8%)	15 (12%)
Non-LRTD only	15 (10%)	7 (5%)

(Table 1 continues in next column)

(Continued from previous column)

Data are n, n (%), or mean (SD), unless otherwise indicated. ITT=intention to treat; all randomised patients who received study drug. BMT=bone marrow transplantation. HSCT=haemopoietic stem cell transplantation. eGFR-MDRD=estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula. mITT=modified intention to treat; ITT patients with proven or probable invasive mould disease. LRTD=lower respiratory tract disease. *Other regions consist of Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand, and Turkey. †Primary underlying disease in ≥1% of patients. ‡As assessed by the data review committee. §Fungal species were isolated from some patients in this group but these organisms were considered as colonisers. No mycological evidence does not include patients with possible invasive mould disease. ¶No further information. ‖Two consecutive serum galactomannan values ≥0·5 or at least one serum galactomannan value ≥0·7, as defined in the trial protocol.

Table 1: **Demographics and baseline characteristics**

test. Continuous data were summarised descriptively. Categorical data were summarised by number and percentage of patients within each category. All data analyses were done with SAS version 9.3.

This trial is registered with ClinicalTrials.gov, number NCT00412893.

	Isavuconazole	Voriconazole	Adjusted treatment difference (95% CI)*
All-cause mortality			
ITT population	258	258	
Day 42 all-cause mortality	48 (19%)	52 (20%)	−1·0% (−7·8 to 5·7)
Deaths	45 (17%)	50 (19%)	..
Unknown survival status†	3 (1%)	2 (1%)	..
Day 84 all-cause mortality	75 (29%)	80 (31%)	−1·4% (−9·2 to 6·3)
Deaths	72 (28%)	75 (29%)	..
Unknown survival status†	3 (1%)	5 (2%)	..
mITT population	143	129	
Day 42 all-cause mortality	28 (20%)	30 (23%)	−2·6% (−12·2 to 6·9)
Day 84 all-cause mortality	43 (30%)	48 (37%)	−5·5% (−16·1 to 5·1)
myITT population	123	108	
Day 42 all-cause mortality	23 (19%)	24 (22%)	−2·7% (−12·9 to 7·5)
Day 84 all-cause mortality	35 (28%)	39 (36%)	−5·7% (−17·1 to 5·6)
Possible invasive mould disease	88	108	
Day 42 all-cause mortality	15 (17%)	19 (18%)	−0·5% (−12·3 to 11·2)‡
Day 84 all-cause mortality	24 (27%)	27 (25%)	2·3% (−11·2 to 15·8)‡
DRC-assessed response (mITT population)			
Overall response at EOT§	143	129	
Success	50 (35%)	47 (36%)	1·6% (−9·3 to 12·6)
Complete	17 (12%)	13 (10%)	..
Partial	33 (23%)	34 (26%)	..
Failure¶	93 (65%)	82 (64%)	..
Stable	42 (29%)	33 (26%)	..
Progression	51 (36%)	49 (38%)	..
Clinical response at EOT§	85/137 (62%)	73/121 (60%)	0·4% (−10·6 to 11·5)
Mycological response at EOT§	54/143 (38%)	53/129 (41%)	3·8% (−7·4 to 15·1)
Radiological response at EOT§	41/141 (29%)	42/127 (33%)	5·7% (−4·9 to 16·3)

Data are n, n (%), or n/N (%).The non-inferiority margin was 10% for adjusted treatment differences between isavuconazole and voriconazole; an upper 95% CI less than 10% suggests that isavuconazole is non-inferior to voriconazole. ITT=intention to treat; all randomised patients who received study drug. mITT=modified intention to treat; ITT patients with proven or probable invasive mould disease. myITT=mycological intention to treat; mITT patients with proven or probable invasive aspergillosis. EOT=end of treatment. *Isavuconazole minus voriconazole for all-cause mortality; voriconazole–isavuconazole for overall, clinical, mycological, and radiological responses. †Patients with unknown survival status were counted as deaths. ‡Crude treatment difference (isavuconazole minus voriconazole) was calculated for possible invasive mould disease and its 95% CI was based on a normal approximation. §Assessed in the ITT population. Favourable mycological response was defined as eradication or presumed eradication. ¶Death or patients with missing information assumed not to have achieved treatment success.

Table 2: **Efficacy outcomes**

Role of funding source

The funders of the study, Astellas Pharma Global Development and Basilea Pharmaceutica International, were involved in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 7, 2007, and March 28, 2013, we recruited patients from 102 centres from 26 countries located across North and South America, Europe, the Middle East, southeast Asia, east Asia, and Pacific regions. 532 patients gave consent, of whom 527 were randomly assigned. 11 patients did not receive any study drug (five did not meet entry criteria, four withdrew consent, and two died), and were excluded from the ITT population, which included 516 patients (n=258 for each treatment group; figure 1). The mITT population consisted of 143 patients in the isavuconazole and 129 patients in the voriconazole group. The myITT population included 123 patients in the isavuconazole group and 108 patients in the voriconazole group.

Baseline demographics and underlying disorders in the ITT population are shown in table 1; there were fewer men in the isavuconazole group and more patients with acute myeloid leukaemia in the voriconazole group. The most common underlying disorder was haematological malignant disease (433 patients; 84%). 105 (20%) patients were recipients of allogeneic haemopoietic stem cell transplantation, and 338 (66%) had neutropenia. The mITT baseline characteristics were similar to those in the ITT population (data not shown).

At baseline, as assessed by the data review committee, 65 (13%) patients had proven invasive mould disease and 207 (40%) had probable invasive mould disease. Possible invasive mould disease was diagnosed in 196 (38%) patients; 48 (9%) had no evidence of invasive mould disease. When *Aspergillus* was cultured as the only mould at baseline, *A fumigatus* (n=53), *A flavus* (n=22), *A niger* (n=8), and *A terreus* (n=6) were the most commonly identified species.

Total treatment duration for the safety population was similar to that of the ITT population. The median durations of total dosing for isavuconazole were 45 days (IQR 13–83; five intravenous, 60 oral) and for voriconazole were 47 days (IQR 13–83; five intravenous, 53 oral). 400 (78%) patients switched from intravenous to oral dosing (194 for isavuconazole and 206 for voriconazole). At day 14, isavuconazole trough plasma concentrations ranged from 813·1 ng/mL to 9952·5 ng/mL, with a mean of 3354 ng/mL (SD 1816 ng/mL) (appendix).

Of 258 patients who received isavuconazole, 118 completed treatment and 140 discontinued treatment. 170 completed follow-up (28 days after end of treatment), and 88 discontinued the study. Of 258 patients who received voriconazole, 120 completed treatment and 138 discontinued treatment. 155 patients completed follow-up and 103 discontinued the study.

For the primary efficacy endpoint, all-cause mortality from first dose of study drug to day 42 in the ITT population was 19% (48 patients) for isavuconazole and 20% (52 patients) for voriconazole (adjusted treatment difference –1·0%, 95% CI –7·8 to 5·7; table 2). The study met the primary objective of demonstrating non-inferiority of isavuconazole versus voriconazole, because the upper limit of the 95% CI (5·7%) was lower than the prespecified 10% non-inferiority margin. All-cause mortality from first dose of study drug to day 42 across the mITT and myITT subpopulations supported this

conclusion (table 2). No treatment-by-subgroup factor interaction was noted according to the prespecified significance value of p<0·15.

For the per-protocol analysis, all-cause mortality from first dose of study drug to day 42 was 15% (26 of 172 patients) for isavuconazole and 18% (31 of 175 patients) for voriconazole (adjusted treatment difference –2·6%, 95% CI –10·3 to 5·1).

For the key secondary efficacy endpoint, overall response at end of treatment (as assessed by the data review committee) in the mITT population was similar for isavuconazole and voriconazole (complete response in 35% [50/143] patients *vs* 36% [47/129]; table 2). Clinical, mycological, and radiological responses at end of treatment, as assessed by the data review committee, were similar in the mITT population (table 2). 31 patients in the isavuconazole group and 29 patients in the voriconazole group were assumed to have not achieved treatment success because they had no imaging after baseline.

Mortality from first dose of study drug to day 84 using the Kaplan-Meier method was similar between treatment groups in both the ITT population (treatment difference –1·1%, 95% CI –8·9 to 6·7; figure 2) and the mITT population (–5·7%, 95% CI –16·9 to 5·5; appendix). An analysis of mortality using the revised galactomannan criteria is provided in the appendix.

Nearly all patients in the safety population had at least one treatment-emergent adverse event (247 [96%] receiving isavuconazole and 255 [98%] receiving voriconazole; p=0·122). The five most common events that occurred in at least 5% of patients in either group were nausea, vomiting, diarrhoea, pyrexia, and hypokalaemia (appendix).

Proportions of patients with treatment-emergent adverse events by system organ classes were similar for most categories (table 3), although isavuconazole-treated patients had a significantly lower frequency of hepatobiliary disorders, eye disorders, and skin or subcutaneous tissue disorders. The proportion of patients with serious treatment-emergent adverse events was similar between treatment groups.

Significantly fewer patients reported events considered drug-related by the investigator for isavuconazole than for voriconazole (109 [42%] *vs* 155 [60%]; p<0·001). Additionally, fewer isavuconazole-treated patients experienced drug-related treatment-emergent adverse events within the following system organ classes: hepatobiliary disorders, laboratory investigations, eye disorders, and psychiatric disorders. Permanent drug discontinuation due to treatment-emergent adverse events were less common with isavuconazole (37 [14%] *vs* 59 [23%]). Permanent drug discontinuation due to drug-related adverse events was lower for isavuconazole than for voriconazole (21 [8%] *vs* 35 [14%]).

Differences between isavuconazole and voriconazole for the overall analysis of treatment-emergent adverse events and serious treatment-emergent adverse events were consistent with those of the subgroup analysis by age, sex, race, ethnic origin, geographical region, allogeneic transplantation, active malignancy status, and neutropenia (data not shown). Analyses of other safety parameters, including laboratory parameters and ECG, revealed no clinically relevant trends (data not shown).

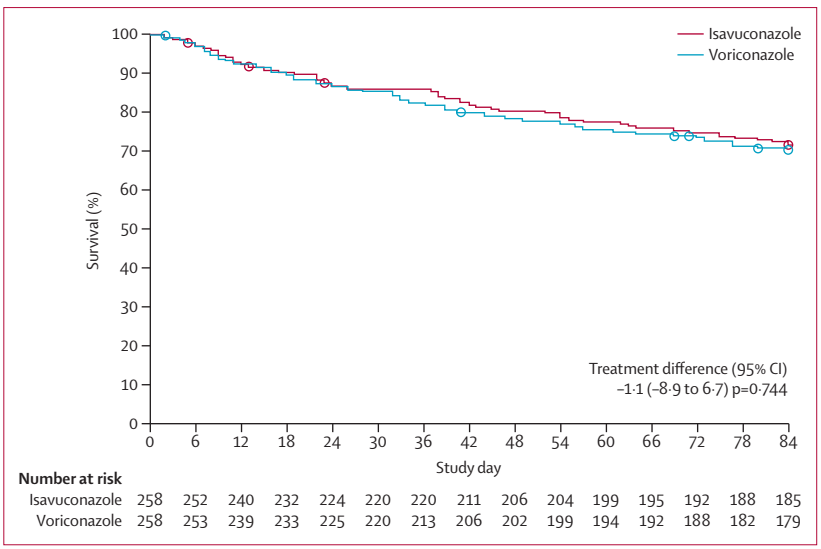

Figure 2: **Survival from first dose of study drug to day 84**
Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

In a post-hoc analysis of the strictly defined intention-to-treat population (all patients randomly assigned, irrespective of whether they received the study drug), all-cause mortality from first dose of study drug to day 42 was 20% (53 of 263 patients) for isavuconazole and 22% (57 of 264 patients) for voriconazole (adjusted treatment difference –1·1%, 95% CI –7·9 to 5·7).

Discussion

In this double-blind, randomised trial, we compared the efficacy and safety of intravenous and oral formulations of two mould-active azoles for the treatment of invasive aspergillosis and other mould infections. Our study demonstrates that isavuconazole is non-inferior to voriconazole in patients suspected of having invasive mould disease, but showed significantly fewer drug-related adverse events and fewer drug discontinuations.

Our primary analysis, 42-day mortality in the ITT population, met the prespecified non-inferiority margin of 10% (adjusted treatment difference –1·0%, 95% CI –7·8 to 5·7). The equivalent analysis in the mITT population, consisting of patients with proven or probable invasive mould disease, was –2·6% (95% CI –12·2 to 6·9); because the upper 95% CI was less than 10%, this finding also supports non-inferiority of isavuconazole versus voriconazole in this population. However, the study was powered to show a non-inferiority margin for the primary endpoint only; the denominator

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶
Immune system disorders	20 (8%)	25 (10%)	0·533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0·101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0·846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0·373
Endocrine disorders	5 (2%)	3 (1%)	0·503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0·685
Social circumstances	0	1 (<1%)	>0·999

Coded in MedDRA 12.1. Adverse events (preferred terms) reported in safety population (all patients who received first dose of study drug). *Rash, 17/257 (7%) *vs* 28/259 (11%); erythema, 9/257 (4%) *vs* 15/259 (6%); skin lesion, 4/257 (2%) *vs* 8/259 (3%); and drug eruption, 3/257 (1%) *vs* 11/259 (4%). †Hallucinations, 6/257 (2%) *vs* 11/259 (4%); visual hallucinations, 3/257 (1%) *vs* 11/259 (4%); and agitation, 2/257 (1%) *vs* 7/259 (3%). ‡Visual impairment, 4/257 (2%) *vs* 19/259 (7%); photophobia, 2/257 (1%) *vs* 6/259 (2%); reduced visual acuity, 1/257 (<1%) *vs* 6/259 (2%); and retinal haemorrhage 0/257 (0%) *vs* 5/259 (2%). §Hyperbilirubinaemia, 5/257 (2%) *vs* 10/259 (4%); abnormal hepatic function, 4/257 (2%) *vs* 9/259 (3%); jaundice, 1/257 (<1%) *vs* 6/259 (2%); and cholestasis, 1/257 (<1%) *vs* 6/259 (2%). ¶Statistical significance at p≤0·05 (Fisher's exact test).

Table 3: **Treatment-emergent adverse events by system organ class**

was substantially smaller in the mITT population (n=272) than in the ITT population (n=516), which resulted in widened 95% CIs. Nevertheless, the upper 95% CI was also less than 10% for the mITT, myITT, per-protocol, and (post-hoc) strictly defined intention-to-treat populations, thereby providing strong support for the non-inferiority of isavuconazole versus voriconazole.

Voriconazole is currently recommended for the primary treatment of invasive aspergillosis on the basis of results from a study in which voriconazole significantly improved survival compared with amphotericin B deoxycholate.[21] In real-life registries, the first-line use of voriconazole has been consistently associated with improved response and decreased mortality attributable to invasive aspergillosis compared with other mould-active agents.[2,23] Voriconazole is also recommended for the primary treatment of some rare mould infections, but is not active against Mucorales.[9] It displays highly variable non-linear pharmacokinetics in adults, which has triggered recommendations for therapeutic drug monitoring.[10,24] By contrast, isavuconazole, which has activity against Mucorales,[13] demonstrates predictable and linear pharmacokinetics with low interpatient variability, making it an attractive alternative.[25]

Similar to a recent study in invasive aspergillosis, we used all-cause mortality at 6 weeks as the primary outcome measure.[26] This outcome was chosen because it provides the most objective and reproducible effect of therapy, and approximates best the attributable mortality, because deaths due to competing causes occur increasingly after 6 weeks.[27]

Overall response, our secondary endpoint, is traditionally used as the primary endpoint, but is less rigorous and more subjective. When analysing individual components of the data review committee-assessed overall response in our study, an inconsistency was noted between clinical response and radiological response rates. Indeed, as described previously,[28] radiographic evidence of response, the key driver of overall response, lagged behind clinical improvement. Mycological and radiological responses for patients with missing data were counted as failures, thereby ensuring any bias that was introduced was conservative.

In a large phase 3 trial of voriconazole, the overall response at week 12 was 53% (76/144) in the voriconazole group (median treatment duration for voriconazole 77 days [range 2–84]).[21] The overall response at end of treatment in our study was 36% (47/129) for voriconazole (median treatment duration 50 days [range 1–88]). This difference could be accounted for by different definitions of neutropenia (at baseline), inclusion of possible cases in the previous study, and by the more stringent response criteria of the SECURE trial.[29] It should be noted that the all-cause mortality rates in both studies were similar.[21]

As in previous studies,[26,30] patients with possible invasive mould disease were enrolled to include early diagnoses and provide early therapy. However, confirmation of invasive mould disease can take up to a week or may not be possible at all. With all available diagnostic data from the first study week, the data review committee confirmed that 53% of the ITT population had proven or probable invasive mould disease and could be included in the mITT analysis. Importantly, as per our protocol but contrary to current international consensus definitions[18] and studies mentioned previously,[26,30] galactomannan positivity of broncho-alveolar fluid alone was not accepted to upgrade possible cases to probable disease. Many ITT patients could not be included in the mITT population, which, similar to previous trials, might have increased the probability of meeting the non-inferiority margin. However, examination of the mITT population suggests that the non-inferiority margin would have been met in that population. Nevertheless, enrolment of patients with possible invasive mould disease at study entry reflects the real-life strategy of early initiation of antifungal treatment.

The most important differentiating feature between isavuconazole and voriconazole in the current study was the tolerability and safety profile of isavuconazole, which could allow safer therapy. Voriconazole therapy is characterised by a narrow therapeutic window and an established association between elevated concentrations and neurotoxic,[31] hepatic, and visual adverse events.[32] These adverse events, although usually reversible, often lead to premature discontinuation of the drug. Of the drug-related hepatobiliary adverse events reported in our study, 26 (10%) were noted in the voriconazole group compared with five (2%) in the isavuconazole group. In this study, key adverse events known to be related to voriconazole (including eye, hepatic, and skin disorders) and discontinuations due to adverse events were significantly less common among isavuconazole-treated patients. Given the double-blind nature of the study, this suggests a true difference in the safety features of the two azoles. Whether the higher proportion of adverse events with voriconazole was due to supratherapeutic drug exposure cannot be excluded without therapeutic drug monitoring; however, the effect of therapeutic drug monitoring on the incidence of these adverse events remains speculative.

The generalisability of our study is limited because of the exclusion of patients with AIDS, abnormal liver or renal function, and those receiving antifungal prophylaxis with a mould-active azole. Additionally, few patients with rare disorders for invasive mould disease were enrolled in the study.

During the conduct of this study, therapeutic drug monitoring for voriconazole—aimed at improving response by individualising dosage regimens, preventing drug-related adverse events, and early discontinuation—became the standard of care in some institutions. This study used the labelled dose of voriconazole and did not address the comparative efficacy of isavuconazole versus voriconazole administered at higher oral doses or with therapeutic drug monitoring. However, on the basis of the predictable and linear pharmacokinetics,[11] no evidence seems to suggest that therapeutic drug monitoring is required for isavuconazole.

We conclude that isavuconazole is non-inferior to voriconazole for the primary treatment of suspected invasive mould disease, with substantially fewer drug-related adverse events and discontinuations.

Contributors

JAM, KAM, TFP, OAC, MA, RH, D-GL, RMM, A-HS-H, and AJU proposed the key elements of study design. KAM, TFP, DPK, OAC, DN, RH, D-GL, VAM, GRT, RMM, A-HS-H, BZ, and AJU provided critical review of draft protocol and made significant contributions to the design. KAM, TFP, DPK, OAC, EJB, DN, RH, D-GL, VAM, GRT, BZ, and AJU had an advisory role on the study and provided significant direction to study development and conduct. JAM was the principal coordinating investigator; other investigators on this study were IIR, OAC, GR, MA, JWB, MG, WJH, RH, MK, D-GL, OL, IO, DS, and GRT. ML was the statistical lead on the study who oversaw the analyses. TFP, DPK, EJB, WH, OL, VAM, SS, and AJU were members of the data review committee. All authors were involved in the interpretation of data, drafting the work or revising it critically for important intellectual content, approved the final version of the publication and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

JAM reports grants and personal fees from Bio-Rad, personal fees and non-financial support from Astellas and Basilea, and grants, personal fees and non-financial support from Gilead Sciences, Merck Sharp and Dohme, and Pfizer, Inc. during the conduct of the study. IIR participated in an International Speakers' Bureau for Pfizer, outside the submitted work. KAM reports personal fees from Astellas during the conduct of the study; personal fees from Chimerix, Cidara, Genentech and Merck, and grants and personal fees from Astellas, outside the submitted work. In addition, KAM has a patent (diagnostics for aspergillosis) licensed to MycoMed Technologies. TFP reports personal fees from Astellas during the conduct of the study; grants from Astellas, personal fees from Pfizer, Scynexis, Toyama, and Viamet, and grants and personal fees from Merck, outside the submitted work. OAC is supported by the German Federal Ministry of Research and Education, has received research grants from 3M, Actelion, Astellas, AstraZeneca, Basilea, Bayer, Celgene, Cubist/Optimer, Duke University (NIH UM1AI104681), Genzyme, Gilead, GSK, Leeds University, Merck/MSD, Miltenyi, Pfizer, Quintiles, Viropharma, is a consultant to Anacor, Astellas, Basilea, Cidara, Da Volterra, Daiichi Sankyo, F2G, Genentech, Gilead, Merck/MSD, Merck Serono, Pfizer, Sanofi Pasteur, Scynexis, Seres, Summit, Vical, Vifor, and received lecture honoraria from Astellas, Basilea, Gilead, Merck/MSD, and Pfizer. EJB was a member of the Data Review Committee for Astellas, after the conduct of the study; EJB also reports personal fees from Cidara, Gilead, GLY-Pharma, and Pfizer, outside the submitted work. GR reports grants from Astellas during the conduct of the study, and grants from Pfizer, MSD, Gilead, and AstraZeneca, outside the submitted work. DN reports personal fees from Astellas during the conduct of the study; personal fees from Astellas and Roche Molecular Diagnostics, outside the submitted work; DN is currently an employee of Roche Diagnostics. JWB reports personal fees from Astellas, Merck, and Pfizer, outside the submitted work. WJH reports personal fees from Astellas, Basilea, and Gilead Sciences, and grants and personal fees from MSD Sharp & Dohme/Merck, and Pfizer, outside the submitted work. RH reports personal fees from Astellas, Basilea, Gilead Sciences, MSD, and Schering-Plough, and grants and personal fees from Pfizer during the conduct of the study. WH reports grants and personal fees from Astellas, F2G, and Pfizer, outside the submitted work. MK reports participation on advisory boards for Astellas and Pfizer, outside the submitted work. D-GL reports grants and personal fees from Astellas, Gilead Sciences, MSD, Pfizer, and Yuhan, outside the submitted work. OL reports grants from Astellas during the conduct of the study, and personal fees from Gilead, Pfizer, and Merck, outside the submitted work. VAM was a member of the Data Review Committee for Astellas, after the conduct of the study. DS reports grants from Astellas during the conduct of the study; grants, personal fees and non-financial support from Pfizer, as well as personal fees and non-financial support from MSD, outside the submitted work. SS reports grants from Astellas during the conduct of the study; grants from Astellas, Chimerix, Merck, Pfizer, Scynexis, and Viropharma, and personal fees from the Mycoses Study Group Education and Research Consortium, outside the submitted work. GRT was a member of the Data Review Committee, after the conduct of the study; he reports grants from Pfizer and Merck, outside the submitted work. AJU received personal fees and fees for travel, speakers' bureau and consultancy from Basilea, and grants, personal fees, and fees for travel, speakers' bureau and consultancy from Astellas during the conduct of the study; grants, personal fees and fees for travel, speakers' bureau and consultancy from MSD, Gilead Sciences and Pfizer, and personal fees from Boehringer Ingelheim, outside the submitted work. ML, RMM, and BZ are employees of Astellas Pharma Global Development, Inc. A-HS-H is an employee of Basilea Pharmaceutica International Ltd. DPK, MA, MG, and IO declare no competing interests.

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References

1 Bitar D, Lortholary O, Le Strat Y, et al. Population-based analysis of invasive fungal infections, France, 2001-2010. *Emerg Infect Dis* 2014; **20:** 1149–55.

2 Lortholary O, Gangneux JP, Sitbon K, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007). *Clin Microbiol Infect* 2011; **17:** 1882–89.

3 Lanternier F, Lortholary O. Liposomal amphotericin B: what is its role in 2008? *Clin Microbiol Infect* 2008; **14** (suppl 4)**:** 71–83.

4 Enoch DA, Idris SF, Aliyu SH, Micallef C, Sule O, Karas JA. Micafungin for the treatment of invasive aspergillosis. *J Infect* 2014; **68:** 507–26.

5 Herbrecht R, Maertens J, Baila L, et al. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study. *Bone Marrow Transplant* 2010; **45:** 1227–33.

6 Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; **44:** 2–12.

7 Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46:** 327–60.

8 Maertens J, Marchetti O, Herbrecht R, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 update. *Bone Marrow Transplant* 2011; **46:** 709–18.

9 Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. *Clin Microbiol Infect* 2014; **20** (suppl 3)**:** 27–46.

10 Mikulska M, Novelli A, Aversa F, et al. Voriconazole in clinical practice. *J Chemother* 2012; **24:** 311–27.

11 Schmitt-Hoffmann A, Roos B, Heep M, et al. Single-ascending-dose pharmacokinetics and safety of the novel broad-spectrum antifungal triazole BAL4815 after intravenous infusions (50, 100, and 200 milligrams) and oral administrations (100, 200, and 400 milligrams) of its prodrug, BAL8557, in healthy volunteers. *Antimicrob Agents Chemother* 2006; **50:** 279–85.

12 Lepak AJ, Marchillo K, Vanhecker J, Andes DR. Isavuconazole (BAL4815) pharmacodynamic target determination in an in vivo murine model of invasive pulmonary aspergillosis against wild-type and cyp51 mutant isolates of *Aspergillus fumigatus*. *Antimicrob Agents Chemother* 2013; **57:** 6284–89.

13 Luo G, Gebremariam T, Lee H, Edwards JE Jr, Kovanda L, Ibrahim AS. Isavuconazole therapy protects immunosuppressed mice from mucormycosis. *Antimicrob Agents Chemother* 2014; **58:** 2450–53.

14 Lepak AJ, Marchillo K, VanHecker J, Diekema D, Andes DR. Isavuconazole pharmacodynamic target determination for Candida species in an in vivo murine disseminated candidiasis model. *Antimicrob Agents Chemother* 2013; **57:** 5642–48.

15 Espinel-Ingroff A, Chowdhary A, Gonzalez GM, et al. Multicenter study of isavuconazole MIC distributions and epidemiological cutoff values for the *Cryptococcus neoformans-Cryptococcus gattii* species complex using the CLSI M27-A3 broth microdilution method. *Antimicrob Agents Chemother* 2015; **59:** 666–68.

16 Astellas Pharma US. Cresemba (isavuconazonium sulfate) prescribing information. 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207500Orig1s000lbl.pdf (accessed Oct 10, 2015).

17 European Medicines Agency. Cresemba (isavuconazole). 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002734/human_med_001907.jsp&mid=WC0b01ac058001d124 (accessed Dec 2, 2015).

18 De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46:** 1813–21.

19 US FDA. Draft guidance on qualification of biomarker—galactomannan in studies of treatments of invasive aspergillosis. 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM420248.pdf (accessed June 16, 2015).

20 Denning DW. Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis* 1996; **23:** 608–15.

21 Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347:** 408–15.

22 Spellberg B, Talbot G. Recommended design features of future clinical trials of antibacterial agents for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis* 2010; **51** (suppl 1)**:** S150–70.

23 Ramos ER, Jiang Y, Hachem R, Kassis C, Kontoyiannis DP, Raad I. Outcome analysis of invasive aspergillosis in hematologic malignancy and hematopoietic stem cell transplant patients: the role of novel antimold azoles. *Oncologist* 2011; **16:** 1049–60.

24 Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis* 2012; **55:** 1080–87.

25 Falci DR, Pasqualotto AC. Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections. *Infect Drug Resist* 2013; **6:** 163–74.

26 Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med* 2015; **162:** 81–89.

27 Wingard JR, Ribaud P, Schlamm HT, Herbrecht R. Changes in causes of death over time after treatment for invasive aspergillosis. *Cancer* 2008; **112:** 2309–12.

28 Miceli MH, Maertens J, Buve K, et al. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: proof of principle, description, and clinical and research implications. *Cancer* 2007; **110:** 112–20.

29 Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. *Clin Infect Dis* 2008; **47:** 674–83.

30 Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis* 2007; **44:** 1289–97.

31 Pascual A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clin Infect Dis* 2012; **55:** 381–90.

32 Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *J Clin Pharmacol* 2006; **46:** 235–43.

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Clinical considerations on posaconazole administration and therapeutic drug monitoring in allogeneic hematopoietic cell transplant recipients

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Abstract

There is a paucity of data on posaconazole (PCZ) dosing and therapeutic-drug-monitoring (TDM) in allogeneic hematopoietic cell transplant recipients (allogeneic-HCTr). This was a 3-year retrospective multicenter study (January 1, 2016 to December 31, 2018) in adult allogeneic-HCTr who received PCZ (intravenously, IV and/or as delayed-release tablet, DRT) as prophylaxis or treatment for ≥7 consecutive days (D) with at least 1-PCZ-level available using data of the Swiss Transplant Cohort Study. The primary objective was to describe the distribution of PCZ-level and identify predictors of therapeutic PCZ-level and associations between PCZ-dosing and PCZ-level. A total of 288 patients were included: 194 (67.4%) and 94 (32.6%) received PCZ as prophylaxis and treatment, respectively, for a median of 90 days (interquartile range, IQR: 42–188.5). There were 1944 PCZ-level measurements performed, with a median PCZ level of 1.3 mg/L (IQR: 0.8-1.96). PCZ-level was <0.7 mg/L in 383/1944 (19.7%) and <1.0 mg/L in 656/1944 (33.7%) samples. PCZ-level was <0.7 mg/L in 260/1317 (19.7%) and <1.0 mg/L in 197/627 (31.4%) in patients who received PCZ-prophylaxis versus treatment, respectively. There were no significant differences in liver function tests between baseline and end-of-treatment. There were nine (3.1%) breakthrough invasive fungal infections (bIFI), with no difference in PCZ levels between patients with or without bIFI. Despite a very intensive PCZ-TDM, PCZ-levels remain below target levels in up to one-third of allogeneic-HCTr. Considering the low incidence of bIFI observed among patients with PCZ levels in the targeted range, our data challenge the clinical utility of routine universal PCZ-TDM.

Key words: posaconazole, therapeutic drug monitoring, allogeneic hematopoietic cell transplant recipients, antifungal prophylaxis, antifungal treatment.

Introduction

Posaconazole (PCZ) has been approved for the prophylaxis of invasive fungal infections (IFI) in allogeneic hematopoietic cell transplant (HCT) recipients with graft-versus-host disease (GvHD) requiring treatment with high-dose steroids and can be used as salvage therapy for patients with invasive mold infections (IMI).[1–4] Posaconazole is available as an intravenously (IV) administered formulation, an oral (PO) suspension, and more recently, as a delayed-release tablet (DRT). Target PCZ target concentrations of 0.7 and 1.0 mg/L for prophylaxis and treatment, respectively, have been proposed and endorsed by international societies.[5,6] Data on therapeutic drug monitoring (TDM) of PCZ-DRT obtained from a phase-3 prospective prophylaxis clinical trial using a maintenance dose of 300 mg once daily demonstrated a steady-state Cmin ≥0.7 mg/L in 90% of subjects.[7] Similarly, small retrospective studies have shown that >90% of patients on the DRT formulation achieve target blood levels.[8–11]

However, there is a paucity of data on PCZ dosing, TDM, and possible associations with efficacy and toxicity from well-described real-life paradigms. Furthermore, there are no well-defined guidelines to inform clinicians on dose adjustments required to achieve therapeutic PCZ concentrations. In clinical practice, incremental dose adjustments by 100 mg are commonly used with successful outcomes, most of the times.[12] We conducted a retrospective multicenter cohort study in allogeneic HCT recipients using data of the Swiss Transplant Cohort Study (STCS) to describe the PCZ dosing and TDM.

Methods

Study design and inclusion/exclusion criteria

The STCS is a multicenter cohort study prospectively enrolling >95% of allogeneic HCT recipients in all Swiss HCT-centers between 2009 and 2018.[13] We performed a 3-year retrospective observational cohort study of all patients, who received PCZ between January 1, 2016 and December 31, 2018. All adult (≥18 years) allogeneic HCT recipients were included if they received PCZ (IV and/or DRT) as prophylaxis or treatment for a minimum of 7 consecutive days (D) with at least one PCZ level available post-D3 of PCZ administration. For patients who received >1 HCT and/or >1 PCZ courses, data were recorded only for the first allogeneic HCT and/or PCZ-course. Patients were excluded if they received PCZ suspension or PCZ-administration for <7 days and had no PCZ-level available by D3 of PCZ administration. All patients had signed an informed consent form to participate in the STCS. The study was approved by the relevant Ethics Committees.

Data collection

Participants were identified through the STCS and hospital-pharmacy databases. The following data were directly retrieved from the STCS-database: demographics and HCT variables: date of HCT, conditioning, HCT source, donor/recipient (D/R) matching, D/R cytomegalovirus (CMV) serology, engraftment-day, and GvHD ≥ grade-2. The following data were retrieved by chart-review: PCZ administration variables (dose, mode of administration, start/stop dates), PCZ-level values, laboratory data at baseline and by D7, 14, 28, 42, 84, end-of-treatment (EOT), and EOT + D14, including C-reactive protein (CRP), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GT), alkaline phosphatase (ALP), and glomerular filtration rate (GFR).

Definitions

The indication of PCZ intake was either prophylaxis or treatment and was defined based on the indication suggested by the treating physician, as noted in patient charts. For patients with a proven/probable IFI before HCT treated with PCZ, PCZ was considered (secondary) prophylaxis if IFI was diagnosed >100 days pre-HCT and as treatment if the diagnosis was made within 3 months prior to HCT. Proven and probable IFI were diagnosed based on revised consensus guidelines.[14] Breakthrough proven/probable IFI (bIFI) was defined as an IFI diagnosed after ≥7 days of PCZ administration.[15]

Posaconazole TDM

PCZ TDM was performed with high-performance liquid chromatography-mass spectrometry (HPLC/MS) by Chromsystems Instruments & Chemicals (Gräfelfing, Germany) in all centers. There were no established protocols of PCZ TDM and dose adjustment at any of the three centers. Posaconazole TDM and subsequent dose changes were performed as clinically indicated. All centers used the same cutoffs of 0.7 and 1.0 mg/L as PCZ targets for prophylaxis and treatment, respectively.

Objectives

The primary objective was to describe the distribution of PCZ-level in a large contemporary cohort of allogeneic HCT recipients. Secondary objectives included the identification of (a) predictors of therapeutic PCZ-levels, (b) associations between PCZ-dosing and PCZ-level, (c) liver function abnormalities, and (d) bIFI during PCZ-administration.

Statistical analysis

Categorical variables were presented as absolute counts and percentages. Continuous variables were described by median, mean, range of values, and interquartile range (IQR), as appropriate. Categorical and continuous variables were compared with the Fisher's exact and a two-tailed Student's *t*-test, respectively.

Intraindividual and interindividual variability of PCZ concentration was assessed by calculating the median of the coefficient of variation (CV) of all the PCZ-level measured in a single patient and the CV of the average PCZ-level of each patient, respectively. Backward logistic regression analysis was completed on different data points to evaluate variables associated with therapeutic PCZ-concentrations. Variables with a *P*-value < .1 in univariable analyses were included in the multivariable models using backwards stepwise logistic regression. A two-sided *P*-value < .05 was considered statistically significant for all tests. Statistical analysis was performed using STATA 16.0 (StataCorp, College Station, TX).

Results

Patient population and PCZ administration

A total of 288 patients were included in this study: 194 (67.4%) received PCZ as prophylaxis (prophylaxis-group) and 94 (32.6%) as treatment (treatment-group). The baseline patient characteristics are detailed in Table 1. PCZ administration data are presented in Table 2. PCZ was started before and after HCT in 46 (16%) and 242 (84%) patients, respectively. A loading dose was administered in 160 (55.6%) patients. Initial maintenance treatment was administered orally (234, 81.3%) at a dose of 300 mg once daily (268, 93.1%) in the vast majority of patients. Patients received PCZ for a median of 90 days (IQR: 42–188.5): 85 and 140 days, in the prophylaxis and treatment groups, respectively (*P*-value = .06).

Posaconazole TDM

Overall patient population

There were 1944 PCZ-level measurements performed during the study period. The median number of tests per patient was 5 (IQR: 3–8), with a median PCZ-level of 1.3 mg/l (IQR: 0.8-1.96; Figure 1A). Intraindividual and interindividual variability of PCZ concentration was 57.0% and 65.0%, respectively. PCZ-level was <0.7 mg/L in 383/1944 (19.7%) and <1.0 mg/L in 656/1944 (33.7%) of all samples (Table 3). PCZ levels significantly increased from a median of 0.73 mg/L by D5 and 0.91 mg/L by D7 to a median of 1.06 mg/L by D14 (*P*-value < .001) and 1.40 mg/L by D28 (*P*-value < .001; Figure 1B). After D28, the median PCZ level remained stable between 1.35 and 1.50 mg/L without significant changes.

By indication

There were 1317 (67.7%) and 627 (32.3%) PCZ level tests in the PCZ prophylaxis group and treatment group, respectively (Figure 2A). The median number of tests per patient was 5 (IQR: 3–8) and 6 (IQR: 3–9) in the prophylaxis group and treatment group, respectively (*P*-value = .87). PCZ level was <0.7 mg/L in 260/1317 (19.7%) and <1.0 mg/L in 197/627 (31.4%, *P*-value = .10) in the prophylaxis-group and treatment-group, respectively. Overall, the median PCZ-level was lower in patients who received PCZ-prophylaxis (1.26 mg/L, IQR: 0.8-1.85) versus treatment (1.50 mg/L, IQR: 0.8-2.25; *P*-value < 0.001; Figure 2B). There were no significant differences in PCZ levels between the prophylaxis-group and treatment-group between D7 and D180 of PCZ administration (Table 3).

Predictors of PCZ level ≥0.7 mg/L

Baseline ALT >100 IU/L (OR: 5.75, *P*-value = .02) was a significant predictor of PCZ level ≥0.7 mg/L by D7 of PCZ administration, while baseline GFR <100 mL/min/1.73 m^2 (odds ratio, OR: 0.48, *P*-value = 0.02) was negatively associated with PCZ level ≥0.7 mg/L by D7 (Supplementary Table S1). PCZ level ≥0.7 mg/L by D7 was the only and strongest predictor of PCZ-level ≥0.7 mg/L by D14 (OR: 4.93, *P*-value = .001; Supplementary Table S2).

PCZ administration changes

Initial maintenance treatment was administered at 300 mg once daily in 268 (93.1%) patients, followed by 400 mg (17, 5.9%) and 200 mg (3, 1%). By EOT, PCZ was administered at 100, 200, 300, 400, 500, 600, 1000 mg daily in 15 (5.2%), 28 (9.7%), 199 (69.1%), 30 (10.4%), 9 (3.1%), 6 (2.1%), and 1 (0.4%) patients, respectively, when compared to initial treatment (*P*-value = .07; Supplementary Figure S1a). PCZ dose and formulation remained unchanged in 112/288 (38.9%) patients throughout their course, whereas 21 (7.3%) and 155 (53.8%) underwent formulation change only and dose ± formulation change, respectively (Supplementary Figure S1b).

PCZ administration changes and PCZ-TDM

Additional analyses were performed in order to describe the relationship between dose and/or formulation changes and PCZ-level. For those analyses, patients were included if the following data were available: (a) PCZ dose and formulation during the first 365 days, (b) PCZ-level before (±1 days) and 7 (±1) days after change in PCZ dose and/or formulation. A total of 139 patients with 240 doses/formulation changes and available PCZ-level were identified (Supplementary Table S3). There were 43 (17.9%), 116 (48.3%), and 81 (33.8%) sets of data for administration formulation-only changes, increasing, and decreasing doses, respectively.

Administration formulation-only changes

In 43 cases of formulation-only changes, the median PCZ-level before and after PCZ change was 0.81 mg/L (IQR: 0.51, 1.42) and 0.96 mg/L (IQR: 0.66, 1.50; *P*-value = 0.68), respectively.

Table 1. Baseline patient characteristics

	All patients N = 288 (%)	PCZ Prophylaxis N = 194 (%)	PCZ Treatment N = 94 (%)	*P*-value[1]
Demographics				
Age, Mean Years (SD; Range)	51.5 (14.2; 18–76)	51.6 (14.2; 18–76)	50.2 (14.2; 18–73)	.45
Gender, Female	106 (36.8)	72 (37.1)	34 (36.2)	.90
HCT characteristics				
HCT Donor				.14
Matched related	82 (28.5)	50 (25.8)	32 (34.0)	
Matched unrelated	145 (50.3)	106 (54.6)	39 (41.5)	
Mismatched unrelated	23 (8.0)	16 (8.3)	7 (7.5)	
Haploidentical	38 (13.2)	22 (11.3)	16 (17.0)	
HCT source				.10
Bone marrow	55 (19.1)	31 (16.0)	24 (25.5)	
Peripheral blood stem cells	232 (80.6)	162 (83.5)	70 (74.5)	
Cord blood	1 (0.3)	1 (0.5)	0	
Conditioning regimen, Myeloablative	131 (45.4)	103 (53.1)	91 (46.9)	.49
GvHD prophylaxis				.03
Cyclosporine, MMF	115 (40.0)	72 (37.1)	43 (45.7)	
Cyclosporine, Methotrexate	122 (42.4)	83 (42.8)	39 (41.5)	
Tacrolimus, Methotrexate	13 (4.5)	13 (6.7)	0	
Tacrolimus, MMF, Cyclophosphamide	38 (13.1)	26 (13.4)	12 (12.8)	
GvHD ≥ grade 2	144 (50.0)	118 (60.8)	26 (27.7)	<.001
Gastro-intestinal GvHD ≥ grade 2	78 (27.1)	67 (34.5)	11 (11.7)	<.001
CMV donor/recipient serology status				.37
D-R-	89 (30.9)	57 (29.4)	32 (34.0)	
D-R+	65 (22.6)	47 (24.3)	18 (19.2)	
D + R+	106 (36.8)	68 (35.0)	38 (40.4)	
D + R-	28 (9.7)	22 (11.3)	6 (6.4)	
Proven/Probable IFI prior to HCT	59 (20.5)	19 (9.8)	40 (42.6)	<.001
IFI, Median Days before HCT (IQR)	65 (36, 124)	136 (124, 217)	42 (26.5, 66)	<.001
Laboratory values at PCZ initiation				
ANC (mm^3/mL), Median (IQR)[2]	1.95 (0.5, 4.2)	1.9 (0.6, 4)	2.0 (0.23, 4.5)	.53
ALC (mm^3/mL), Median (IQR)[3]	0.37 (0.1, 0.9)	0.36 (0.1, 0.8)	0.46 (0.15, 1.2)	.26
GFR (mL/min/1.73m^2), Median (IQR)[4]	92 (68, 108)	88 (65, 108)	98 (78, 112)	.13
AST (IU/l), Median (IQR)[5]	23 (17, 35)	23 (17, 37)	23 (16, 35)	.99
ALT (IU/l), Median (IQR)[6]	28.5 (18, 57.5)	30 (19, 61)	26 (18, 49)	.62
g-GT (IU/l), Median (IQR)[7]	72 (41, 159)	81.5 (40, 155)	62 (41, 162)	.64
ALP (IU/l), Median (IQR)[8]	84 (57, 126)	81.5 (56, 116)	87.5 (61.5, 149)	.67
Center				.002
Center 1	122 (42.4)	86 (44.3)	36 (38.3)	
Center 2	96 (33.3)	73 (37.6)	23 (24.5)	
Center 3	70 (24.3)	35 (18.1)	35 (37.2)	

PCZ, Posaconazole; SD, standard deviation; IQR, interquartile range; HCT, hematopoeitic cell transplant; GvHD, graft-versus-host disease; MMF, mycophenolate mofetil; CMV, Cytomegalovirus ; D, donor; R, recipient; IFI, invasive fungal infection; ANC, absolute neutrophil count ; ALC, absolute lymphocyte count; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; IU, international unit.

[1] *P*-value was calculated by t-test and chi-square test for continuous and categorical variables, respectively.

[2] Data on ANC were available for 226 patients in total: 152 and 74 in the prophylaxis and treatment groups, respectively.

[3] Data on ALC were available for 258 patients in total: 173 and 85 in the prophylaxis and treatment groups, respectively.

[4] Data on GFR were available for 273 patients in total: 181 and 92 in the prophylaxis and treatment groups, respectively.

[5] Data on AST were available for 258 patients in total: 177 and 81 in the prophylaxis and treatment groups, respectively.

[6] Data on ALT were available for 272 patients in total: 182 and 90 in the prophylaxis and treatment groups, respectively.

[7] Data on gGT were available for 213 patients in total: 152 and 61 in the prophylaxis and treatment groups, respectively.

[8] Data on ALP were available for 266 patients in total: 178 and 88 in the prophylaxis and treatment groups, respectively.

Table 2. Posaconazole administration data

PCZ variables	All patients N = 288 (%)	PCZ Prophylaxis N = 194 (%)	PCZ Treatment N = 94 (%)	*P*-value[1]
PCZ started before HCT	46 (16)	36 (18.6)	10 (10.6)	
Median days PCZ initiation before HCT (IQR)	12.5 (4, 110)	12 (3, 110)	25 (8, 63)	.86
PCZ started after HCT	242 (84)	158 (81.4)	84 (89.4)	
Median days PCZ initiation after HCT (IQR)	31.5 (15, 135)	35.5 (15, 145)	28.5 (15, 128)	.94
PCZ loading dose	160 (55.6)	103 (53.1)	57 (60.6)	.26
Mode of loading dose, IV	42/160 (26.2)	30/103 (29.1)	12/57 (24.1)	.35
PCZ maintenance dose				
Initial dose, PO	234 (81.3)	152 (78.4)	82 (87.2)	.08
Initial dose mg/day				.20
Initial dose < 300 mg daily	3 (1.0)	3 (1.6)	0	
Initial dose 300 mg daily	268 (93.1)	183 (94.3)	85 (90.4)	
Initial dose 400 mg daily	17 (5.9)	8 (4.1)	9 (9.6)	
Number of dose changes during course				.30
No dose/no mode changes	112 (38.9)	69 (35.6)	43 (45.7)	
No dose/mode changes	21 (7.3)	16 (8.2)	5 (5.3)	
≥1 dose ± mode changes	155 (53.8)	109 (56.2)	46 (49.0)	
PCZ duration				
Median days (IQR)	90 (42, 188.5)	85 (39, 164)	140 (55, 230)	
≥7 days	288 (100)	194 (100)	94 (100)	1.00
≥14 days	278 (96.5)	187 (96.4)	91 (96.8)	1.00
≥28 days	238 (82.6)	158 (81.4)	80 (85.1)	.51
≥42 days	217 (75.4)	144 (74.2)	73 (77.7)	.56
≥84 days	158 (54.9)	99 (51.0)	59 (62.8)	.08
≥100 days	134 (46.5)	81 (41.7)	53 (56.4)	.02
≥180 days	83 (28.8)	47 (24.2)	36 (38.3)	.02
≥365 days	22 (7.6)	13 (6.7)	9 (9.6)	.48

PCZ, Posaconazole; HCT, hematopoeitic cell transplant; IV, intravenous; PO, oral; IQR, interquartile range.
[1] *P*-value was calculated by t-test and chi-square test for continuous and categorical variables, respectively.

Dose increase

In 116 sets of available data, the median PCZ-level before and after PCZ dose-increase was 0.53 mg/L (IQR: 0.35, 0.70) and 0.96 mg/L (IQR: 0.60, 1.50; *P*-value < .001), respectively (Figure 3A). PCZ-level decreased (N: 21) or did not change (N: 1) in 22/116 (19%) and increased in 94 (81%) cases. Dose increases led to higher median post-change PCZ-level between 0.91 and 1.16 mg/L, with the highest median PCZ-level attained with a dose-increase of 50–67% (Figure 3B).

Dose decrease

In 81 sets of data with dose decrease, the median PCZ-level before and after PCZ change was 2.33 mg/L (IQR: 1.50, 3.10) and 1.63 mg/L (IQR: 0.93, 2.29; *P*-value < .001), respectively (Figure 3C). PCZ-level increased in 23 of 81 (28.4%) and decreased in 58 of 81 (71.6%) cases. The baseline median PCZ level was significantly higher in those patients who had a dose-decrease by 33% (2.60 mg/L, *P*-value = 0.001) and 50–67% (2.61 mg/L, *P*-value = 0.04) as compared to 20–25% (1.46 mg/L), respectively (Supplementary Table S4). Dose decreases led to lower median post-change PCZ-level between 1.23 and 1.96 mg/L, with the lowest median PCZ-level achieved with a dose-decrease of 50–67% (Figure 3D).

Liver function tests

To assess the effect of PCZ on liver function, ALT, ALP, and γ-GT for all patients between baseline, end-of-treatment (EOT), and 14 days after EOT (EOT + 14) were compared (Supplementary Figure S2a–c). There were no significant differences in the median (IQR) between baseline, EOT, and EOT + 14 for (a) ALT (baseline-median: 28 IU/L, IQR: 18, 56 versus EOT-median: 38 IU/L, IQR: 23, 64; *P*-value = .12 vs EOT + 14-median: 35 IU/L, IQR: 22, 61; *P*-value = .81), (b) ALP (baseline-median:86 IU/L, IQR: 57, 126 vs EOT-median: 87 IU/L, IQR: 60, 134; *P*-value: 0.53 versus EOT + 14-median: 92 IU/L, IQR: 61, 129; *P*-value: 0.19), and (c) γ-GT (baseline-median: 72 IU/L, IQR: 41, 159 vs EOT-median: 78IU/l, IQR: 38, 176; *P*-value = .70 vs EOT + 14-median: 66 IU/L, IQR: 31, 155; *P*-value = .10).

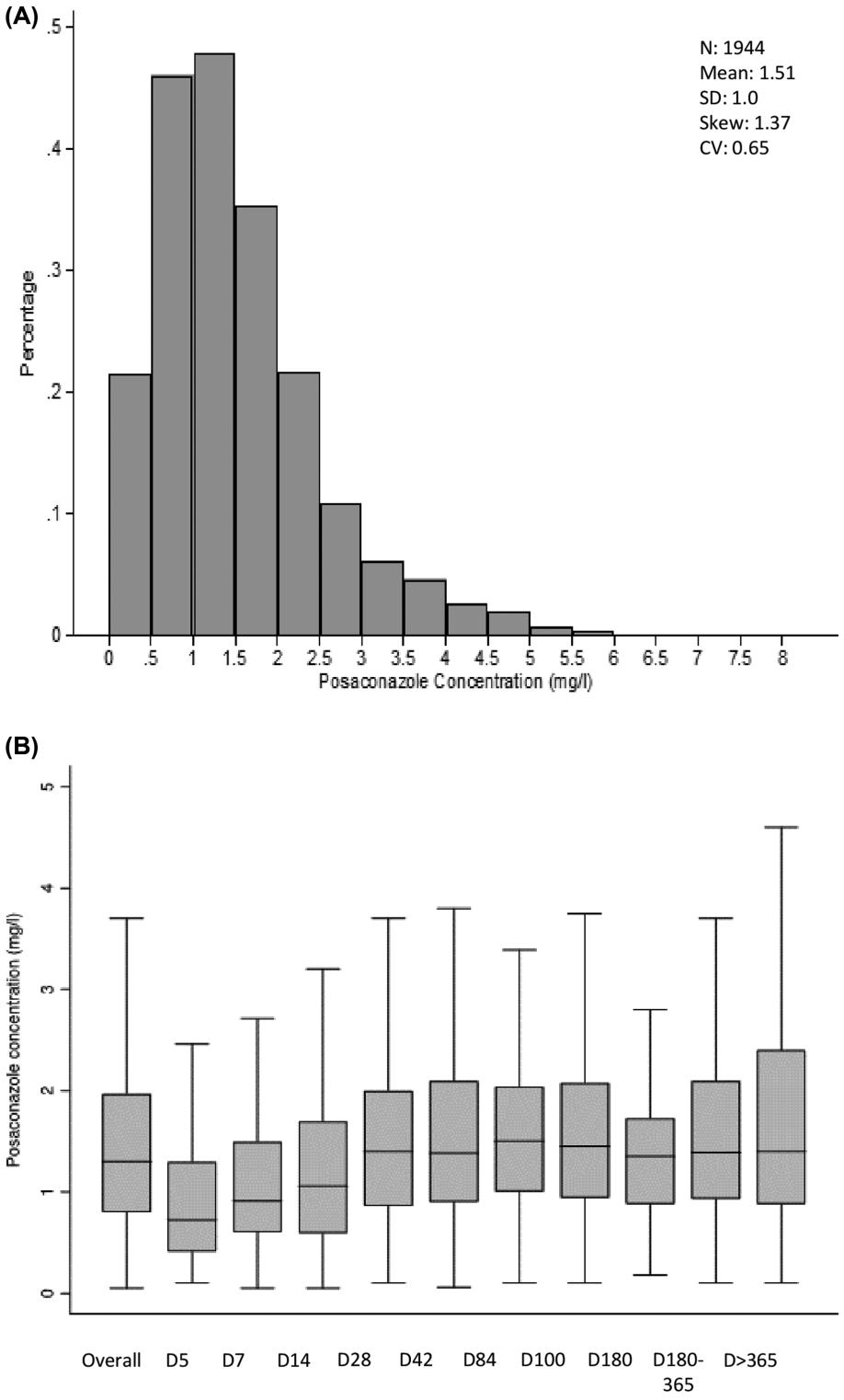

Figure 1. (A) Histogram demonstrating the distribution of posaconazole blood concentrations in the overall cohort. (B) Box-plots of posaconazole blood concentrations on predefined time points of posaconazole administration. Boxes represent the median and 25th and 75th percentiles, whiskers represent the range of maximum and minimum values within the interquartile range. Outliers are not shown. Significant *P*-values calculated by unpaired t-test for the mean values between different time-points for all patients are presented below: D5 to D14: .004, D5 to D28: <.001, D5 to D42: <.001, D5 to D84: <.001, D5 to D100: <.001, D5 to D180: .003, D5 to D180-365: <.001, D5 to D>365: <.001, D7 to D28: <.001, D7 to D42: <.001, D7 to D84: <.001, D7 to D100: <.001, D7 to D180-365: <.001, D7 to D > 365: <.001, D14 to D28: <.001, D14 to D42: <.001, D14 to D84: .002, D14 to D100: .003D14 to D180-365: <.001, D14 to D > 365: <.001.

Table 3. Posaconazole mean/median values in the overall cohort and based on indication (prophylaxis versus treatment) of administration at predefined time-points

	Overall	D5	D7	D14	D28	D42	D84	D100	D180	D 180–365	D > 365
All patients[1]											
Mean (SD)[2]	1.50 (1.0)	0.92 (0.8)	1.12 (0.8)	1.23 (0.8)	1.59 (1.0)	1.59 (1.0)	1.58 (0.9)	1.61 (0.9)	1.39 (0.7)	1.63 (1.0)	1.83 (1.2)
Median	1.30	0.73	0.91	1.06	1.40	1.38	1.50	1.45	1.35	1.39	1.40
IQR	0.80, 1.97	0.40, 1.30	0.60, 1.50	0.59, 1.70	0.86, 2.00	0.90, 2.10	1.00, 2.04	0.90, 2.08	0.88, 1.73	0.93, 2.10	0.88, 2.40
Range	0.05, 8.28	0.10, 4.60	0.05, 4.10	0.05, 3.97	0.10, 5.49	0.06, 4.51	0.10, 4.20	0.10, 4.30	0.18, 3.15	0.10, 5.10	0.10, 5.00
Tests N	1944	86	125	186	155	122	82	62	31	285	83
Prophylaxis[1]											
Mean (SD)	1.44 (0.9)	1.01 (0.8)	1.11 (0.8)	1.21 (0.8)	1.54 (0.9)	1.60 (1.0)	1.53 (0.9)	1.51 (0.9)	1.32 (0.6)	1.46 (0.9)	1.66 (1.1)
Median	1.26	0.90	0.90	1.06	1.40	1.38	1.40	1.40	1.35	1.30	1.40
IQR	0.80, 1.85	0.51, 1.30	0.60, 1.40	0.59, 1.70	0.90, 1.80	0.89, 2.11	0.93, 2.02	0.85, 2.00	0.90, 1.70	0.87, 1.90	0.73, 2.19
Range	0.05. 8.28	0.10, 4.60	0.05, 4.10	0.50, 3.97	0.20, 4.30	0.06, 4.32	0.10, 4.20	0.10, 4.39	0.18, 2.50	0.10, 4.90	0.10, 4.90
Tests N	1317	57	87	132	101	84	60	40	21	189	51
C < 0.7 N (%)	260 (19.7)	23 (40.4)	30 (34.5)	41 (31.1)	10 (9.10)	12 (14.3)	2 (9.10)	6 (15.0)	3 (14.3)	31 (16.4)	9 (17.7)
Treatment[1]											
Mean (SD)	1.66 (1.1)	0.72 (0.7)	1.13 (0.7)	1.26 (0.9)	1.67 (1.2)	1.56 (0.8)	1.71 (0.9)	1.80 (1.0)	1.53 (0.9)	1.98 (1.2)	2.1 (1.4)
Median	1.5	0.72	1.04	1.04	1.46	1.35	1.65	1.80	1.32	1.62	1.68
IQR	0.8, 2.25	0.29, 1.00	0.54, 1.55	0.57, 1.70	0.70, 2.30	0.97, 1.92	1.14, 2.10	1.10, 2.20	0.72, 2.10	1.12, 2.86	1.08, 3.15
Range	0.05, 6.80	0.10, 2.66	0.10, 2.60	0.05,3.80	0.10, 5.49	0.20, 4.51	0.29, 3.80	0.10, 4.30	0.51, 3.15	0.10, 5.10	0.10, 5.00
Tests N	627	29	38	54	54	38	22	22	10	96	32
C < 1.0 N (%)	197 (31.4)	21 (72.4)	19 (50.0)	26 (48.2)	20 (37.0)	10 (26.3)	3 (13.6)	4 (18.2)	3 (30.0)	18 (18.8)	7 (21.9)
P-value[3]	<0.001	0.10	0.88	0.74	0.48	0.85	0.41	0.24	0.43	<0.001	0.11

D: Day, SD: Standard deviation, IQR: Interquartile Range, N: Number, C: Concentration.

D 5, 7, 14, 28, 42, 84, 100, 180, 180–365, and > 365: Posaconazole concentration by day 5, 7 + 2, 14 ± 2, 28 ± 2, 42 ± 2, 84 ± 2, 100 ± 5, 180 ± 5, 180–365, >365 of PCZ administration, respectively.

[1]Values represent posaconazole concentration measured in mg/l.

[2]*P*-values were calculated by unpaired t-test for the mean values between different time-points for all patients are presented below: D5 to D7: .06, D5 to D14: .004, D5 to D28: <.001, D5 to D42: <.001, D5 to D84: <.001, D5 to D100: <.001, D5 to D180: .003, D5 to D180-365: <.001, D5 to D > 365: <.001, D7 to D14: .24, D7 to D28: <.001, D7 to D42: <.001, D7 to D84: <.001, D7 to D100: <.001, D7 to D180: .08, D7 to D180-365: <.001, D7 to D > 365: <.001, D14 to D28: <.001, D14 to D42: <.001, D14 to D84: .002, D14 to D100: .003, D14 to D180: .32, D14 to D180-365: <.001, D14 to D > 365: <.001, D28 to D42: .99, D28 to D84: .96, D28 to D100: .88, D28 to D180: .29, D28 to D180-365: .63, D28 to D > 365: .11, D42 to D84: .96, D42 to D100: .87, D42 to D180: .27, D42 to D180-365: .65, D42 to D > 365: .12, D84 to D100: .84, D84 to D180: .26, D84 to D180-365: .65, D84 to D > 365: .14, D100 to D180: .24, D100 to D180-365: .86, D100 to D > 365: .25, D180 to D180-365: .19, D180 to D > 365: .06, D180-365 to D > 365: .16.

[3]*P*-value were calculated by unpaired *t*-test for the mean values between Prophylaxis- and Treatment-groups at different timepoints.

Breakthrough IFI

There were nine proven/probable bIFIs in the cohort for an incidence of 3.1%, all diagnosed after at least 14 days of posaconazole administration. There were two cases of candidemia due to *C. glabrata* and one case of hepatosplenic candidiasis. Six cases of IMI were diagnosed: two proven (one mixed due to *Rhizomucor pusilus* and *Rhizopus* spp. and one due to *Aspergillus ustus*) and four probable (two due to *Aspergillus* spp., one due to *Rhizomucor pusillus* and one due to an unidentified mold). There was no significant difference in the number of bIFIs between the prophylaxis-group (7/194, 3.6%) and the treatment-group (2/94, 2.1%; *P*-value: 0.72). Duration of PCZ administration was similar between patients with bIFI (mean: 90.8 days, SD: 22.4, median: 86 days, range: 14–195) and no bIFI (mean: 147 days, SD: 152.5, median: 91 days, range: 8, 865; *P*-value: 0.27). There was no difference in the overall PCZ-level mean values between patients with (1.32 mg/L, SD: 0.48, range: 0.4, 1.9) and without (1.47 mg/L, SD: 0.74, range: 0.1, 4.2) bIFI (*P*-value = .55). Patients with bIFI had a median of 3 (range: 1, 13) PCZ-TDM performed prior to bIFI diagnosis. The median PCZ-level before bIFI for all nine patients was 1.31 mg/L (range: 0.4, 1.68). PCZ level was available for all nine cases at a median of 4 days (range: 0–46) before the bIFI was diagnosed. The median of the most recent PCZ level before bIFI diagnosis was 1.1 mg/L (range: 0.4, 1.56). Except for one patient with a PCZ level at 0.4 mg/L measured 9 days prior to bIFI diagnosis, all other patients had a PCZ level between 0.97 and 1.56 mg/L.

Discussion

In this retrospective study with one of the largest contemporary collections of PCZ IV and DRT administration and associated blood concentrations, we observed PCZ levels below the target concentrations in 20–30% of cases, as previously reported.[1,7,8,16–19] More than half of the patients required at least one dose-change, as a response to suboptimal PCZ-levels leading to dose adjustments. In contrast to baseline, when almost all patients received a maintenance dose of 300 mg daily, a large variability of PCZ dose, between 100 and 1000 mg daily, was observed in one-third of patients by EOT. These data suggest that although a universal maintenance dose of 300 mg daily may still be applicable in the large majority of allogeneic HCT recipients, there remains a substantial group of patients requiring dose adjustments in real life.

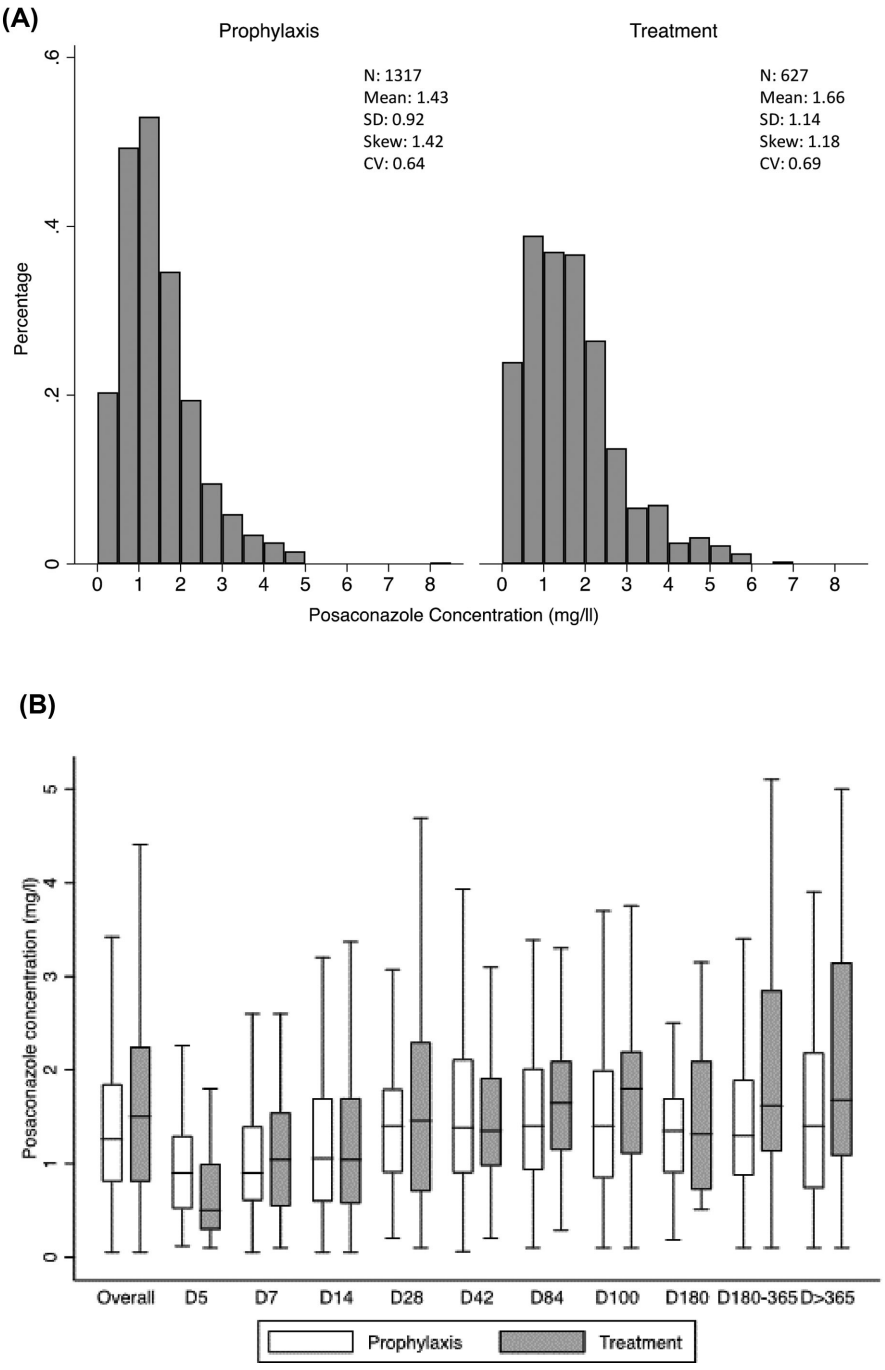

Figure 2. (A) Histogram demonstrating the distribution of posaconazole blood concentrations by indication: prophylaxis versus treatment. (B) Box-plots of posaconazole blood concentrations on predefined time points of posaconazole administration by indication: prophylaxis versus treatment. Boxes represent the median and 25th and 75th percentiles, whiskers represent the range of maximum and minimum values within the interquartile range. Outliers are not shown.

Dose-changes were associated with variable effects on PCZ-levels. In up to one-third of cases a dose change was followed by a counteractive effect, pointing out that dose changes do not always lead to the expected PCZ-level changes. Most dose changes observed in this study were in the range of 20–35%: for instance for a patient receiving 300 mg daily, an increase to 400 mg would be a dose-increase of 33%, while, for a patient receiving 400 mg daily, a decrease to 300 mg would be a dose-decrease of 25%. PCZ-dose increases by 100 mg-increments have been associated with satisfactory PCZ-level elevation.[12] While sufficient in a number of patients, more robust dose changes were frequently required to attain target PCZ levels in this study. Clearly, more data are needed to better appreciate the association and effect of PCZ-dose changes on PCZ levels.

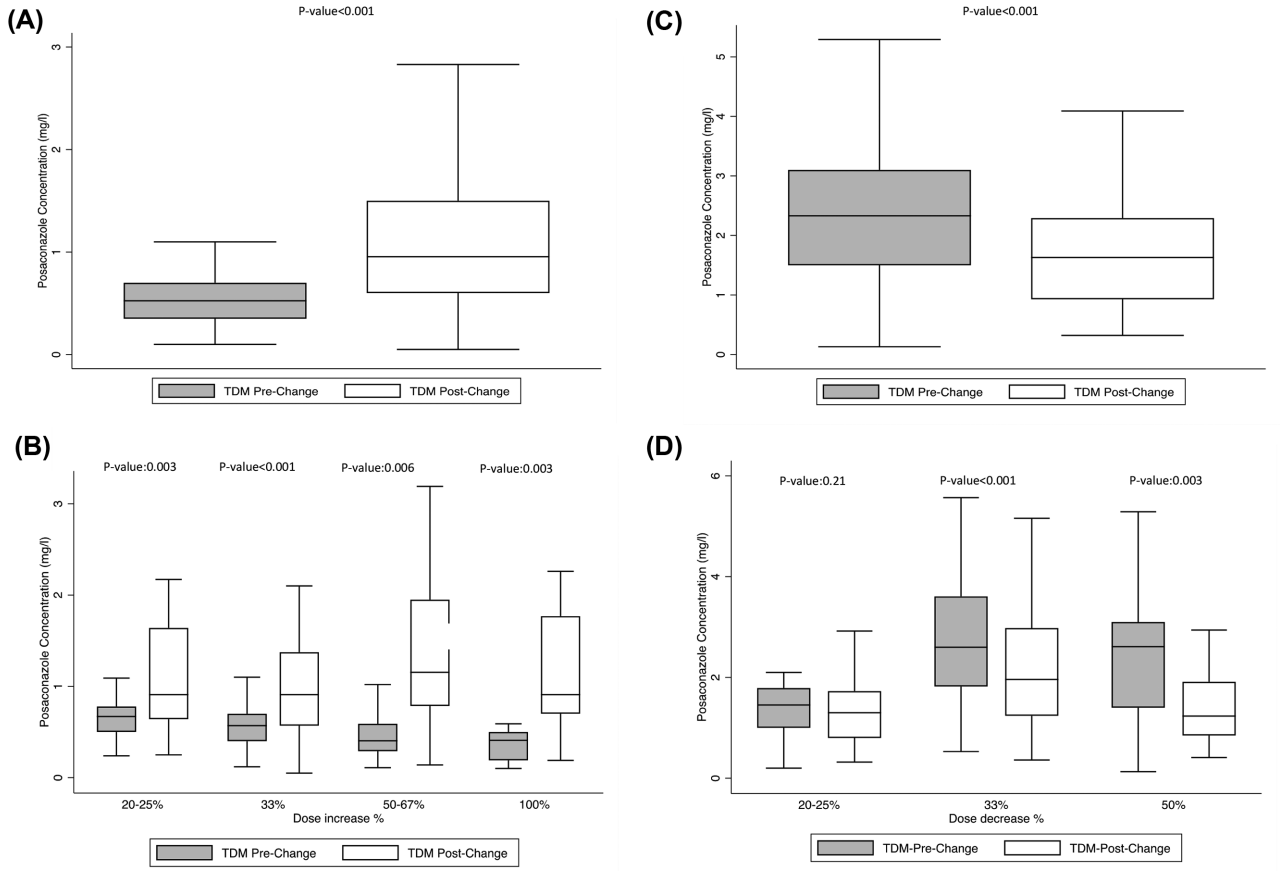

Figure 3. (A) Distribution of posaconazole blood concentrations in patients with dose increases. (B) Distribution of posaconazole blood concentrations in patients with dose increases by percentage of dose increase-categories. (C) Distribution of posaconazole blood concentrations in patients with dose decreases. (D) Distribution of posaconazole blood concentrations in patients with dose decreases by percentage of dose increase-categories. Boxes in Figures 3 a, b, c, and d represent the median and 25th and 75th percentiles, whiskers represent the range of maximum and minimum values within the interquartile range. Outliers are not shown.

More liberal dose increases may lead to higher rates of hepatotoxicity, frequently reported in patients treated with azoles.[20–22] However, liver impairment was reported in only 3% of patients enrolled in the pivotal PCZ-prophylaxis clinical trials and no direct associations between PCZ dose and/or PCZ levels and hepatotoxicity have been demonstrated in pooled analyses.[1,19,23] Similarly, our data did not show any significant differences in liver function between baseline, EOT, and even by 14 days post-EOT. This may reflect the rather normal baseline liver function in the vast majority of patients, modest effect of PCZ on liver function, or represent selection biases: patients with mild to modest liver function test changes during PCZ-administration might have been more likely to sustain PCZ dose changes or transition to another agent, before a significant change was noted.

A small number of bIFI was observed for an overall incidence of approximately 3%, consistent with prior reported rates.[1,19,24] The low rate of bIFI may be explained by the overall higher PCZ concentrations observed in this study, with a median PCZ-level at 1.3 mg/L, higher than 0.49-0.91 mg/L observed in the PCZ-prophylaxis trials.[1,19,25,26] Notably, all but one, patients with bIFI had a PCZ level >0.7 mg/L shortly before the diagnosis of their breakthrough infection.

Target PCZ concentrations of 0.7 and 1.0 mg/L for prophylaxis and treatment, respectively, have been proposed based on post hoc analyses on the exposure-response relationship between PCZ levels and effective IFI prophylaxis, using a composite endpoint of clinical response, in which most cases represented patients who discontinued PCZ prophylaxis for empirical antifungal treatment initiation without confirmation of an IFI.[5] Whether a certain PCZ blood concentration is associated with lower rates of IMI remains largely unknown.[6,27,28] Similarly, the importance of plasma target PCZ concentrations to assure a clinical effect as opposed to adequate PCZ distribution in target tissues is unclear.[23] This is pertinent information for PCZ, a highly protein-bound compound, with multiple-fold higher concentrations in intracellular compartments, including alveolar cells, monocytes and polymorphonuclear cells, as compared to plasma.[29–33] Furthermore, the optimal pharmacokinetic/pharmacodynamic parameters to measure antifungal treatment effect have not –as yet–been well defined.[34,35] The above suggests that while plasma

PCZ-TDM is a useful tool, it may not necessarily be the best surrogate marker of PCZ clinical efficacy. This study was not designed neither powered to assess the clinical utility of PCZ-TDM or the efficacy of PCZ prophylaxis/treatment. However, considering the time, effort and costs invested on PCZ-TDM and dose adjustments based on our observations, low incidence of bIFI, and lack of relevant robust data the question on the utility and clinical significance of universal blood PCZ-TDM may need to be revisited with dedicated clinical trials in the future.[36] Notably, our findings contrast the results of a recently published modeling study, which suggested a potential benefit of routine PCZ-TDM in patient populations with a higher prevalence of subtherapeutic PCZ concentrations.[37] More data to better clarify the optimal PCZ-TDM and target levels are required.

This study has several limitations, including its retrospective observational nature, lack of data on gastrointestinal symptoms and concomitant medication administration, and unavailability of consistent PCZ-TDM, particularly associated with PCZ-dose changes. There were no standardized protocols in place in none of the three centers to perform PCZ TDM. Hence selection bias might have occurred, as patients with more frequent TDM could have been perceived at higher risk for subtherapeutic levels by the treating physician. However, the large number of patients and PCZ-TDM performed in this study have allowed for in-depth analyses of the PCZ-TDM distribution. In conclusion, our data suggest that despite appropriate dosing and close PCZ-TDM, PCZ-levels remain below target for a significant proportion of patients, requiring multiple dose adjustments with not always predictable outcomes. Future studies are required to assess the clinical utility of intensive PCZ-TDM and PCZ dose adjustments in select patient populations.

Supplementary material

Supplementary data are available at *MMYCOL* online.

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Declaration of interest

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References

1. Ullmann AJ, Lipton JH, Vesole DH et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007; 356: 335–347.
2. Walsh TJ, Raad I, Patterson TF et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis*. 2007; 44: 2–12.
3. Greenberg RN, Mullane K, van Burik JA et al. Posaconazole as salvage therapy for zygomycosis. *AAC*. 2006; 50: 126–133.
4. Alexander BD, Perfect JR, Daly JS et al. Posaconazole as salvage therapy in patients with invasive fungal infections after solid organ transplant. *Transplantation*. 2008; 86: 791–796.
5. Jang SH, Colangelo PM, Gobburu JVS. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. *Clin Pharmacol Ther*. 2010; 88: 115–119.
6. Ullmann AJ, Aguado JM, Arikan-Akdagli S et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect*. 2018; 24: e1.
7. Cornely OA, Duarte RF, Haider S et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. *J Antimicrob Chemother*. 2016; 71: 1747.
8. Liebenstein TK, Widmer KM, Fallon MJ. Retrospective analysis of goal drug level attainment of posaconazole for invasive fungal infection prophylaxis in patients with acute myeloid leukemia pre- and post-switch to tablet formulation. *J Oncol Pharm Pract*. 2017: 1078155217722405.
9. Durani U, Tosh PK, Barreto JN, Estes LL, Jannetto PJ, Tande AJ. Retrospective comparison of posaconazole levels in patients taking the delayed-release tablet versus the oral suspension. *Antimicrob Agents Chemother*. 2015; 59: 4914–4918.
10. Cumpston A, Caddell R, Shillingburg A et al. Superior serum concentrations with posaconazole delayed-release tablets compared to suspension formulation in hematological malignancies. *Antimicrob Agents Chemother*. 2015; 59: 4424–4428.
11. Belling M, Kanate AS, Shillingburg A et al. Evaluation of serum posaconazole concentrations in patients with hematological malignancies receiving posaconazole suspension compared to the delayed-release tablet formulation. *Leuk Res Treatment*. 2017; 2017: 3460892.
12. Pham AN, Bubalo JS, Lewis JS. Posaconazole tablet formulation at 400 milligrams daily achieves desired minimum serum concentrations in adult patients with a hematologic malignancy or stem cell transplant *Antimicrob. Agents Chemother*. 2016; 60: 6945–6947.
13. Koller MT, van Delden C, Muller NJ et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. *Eur J Epidemiol*. 2013; 28: 347–355.
14. De Pauw B, Walsh TJ, Donnelly JP et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008; 46: 1813–1821.
15. Cornely OA, Hoenigl M, Lass-Florl C et al. Defining breakthrough invasive fungal infection-Position paper of the mycoses study group education and research consortium and the European Confederation of Medical Mycology. *Mycoses*. 2019; 62: 716–729.
16. Chin A, Pergam SA, Fredricks DN, Hoofnagle AN, Baker KK, Jain R. Evaluation of posaconazole serum concentrations from delayed-release tablets in patients at high risk for fungal infections. *Antimicrob Agents Chemother*. 2017; 61.
17. Tang LA, Marini BL, Benitez L et al. Risk factors for subtherapeutic levels of posaconazole tablet. *J Antimicrob Chemother*. 2017; 72: 2902–2905.
18. Boglione-Kerrien C, Picard S, Tron C et al. Safety study and therapeutic drug monitoring of the oral tablet formulation of posaconazole in patients with haematological malignancies. *J Cancer Res Clin Oncol*. 2018; 144: 127–134.
19. Cornely OA, Maertens J, Winston DJ et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007; 356: 348–359.

20. Moton A, Krishna G, Ma L et al. Pharmacokinetics of a single dose of the antifungal posaconazole as oral suspension in subjects with hepatic impairment. *Curr Med Res Opin*. 2010; 26: 1–7.
21. Tverdek FP, Heo ST, Aitken SL, Granwehr B, Kontoyiannis DP. Real-life assessment of the safety and effectiveness of the new tablet and intravenous formulations of posaconazole in the prophylaxis of invasive fungal infections via analysis of 343 courses. *Antimicrob Agents Chemother*. 2017; 61.
22. Chan SY, Hughes RM, Woo K, Perales MA, Neofytos D, Papanicolaou G. Reasons for voriconazole prophylaxis discontinuation in allogeneic hematopoietic cell transplant recipients: a real-life paradigm. *Med Mycol*. 2020; 58: 1029–1036.
23. Moton A, Krishna G, Wang Z. Tolerability and safety profile of posaconazole: evaluation of 18 controlled studies in healthy volunteers. *J Clin Pharm Ther*. 2009; 34: 301–311.
24. Lionakis MS, Lewis RE, Kontoyiannis DP. Breakthrough invasive mold infections in the hematology patient: current concepts and future directions. *Clin Infect Dis*. 2018; 67: 1621–1630.
25. Krishna G, AbuTarif M, Xuan F, Martinho M, Angulo D, Cornely OA. Pharmacokinetics of oral posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. *Pharmacotherapy*. 2008; 28: 1223–1232.
26. Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. *Pharmacotherapy*. 2007; 27: 1627–1636.
27. Cornely OA, Ullmann AJ. Lack of evidence for exposure-response relationship in the use of posaconazole as prophylaxis against invasive fungal infections. *Clin Pharmacol Ther*. 2011; 89: 351–352.
28. Patterson TF, Thompson GR, Denning DW et al. Practice guidelines for the diagnosis and management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; 63: e1.
29. Conte JE, DeVoe C, Little E, Golden JA. Steady-state intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole in lung transplant recipients. *AAC*. 2010; 54: 3609–3613.
30. Conte JE, Golden JA, Krishna G, McIver M, Little E, Zurlinden E. Intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole at steady state in healthy subjects. *AAC*. 2009; 53: 703–707.
31. Farowski F, Cornely OA, Vehreschild JJ et al. Intracellular concentrations of posaconazole in different compartments of peripheral blood. *AAC*. 2010; 54: 2928–2931.
32. Seyedmousavi S, Bruggemann RJM, Melchers WJG, Verweij PE, Mouton JW. Intrapulmonary posaconazole penetration at the infection site in an immunosuppressed murine model of invasive pulmonary aspergillosis receiving oral prophylactic regimens. *Antimicrob Agents Chemother*. 2014; 58: 2964–2967.
33. Campoli P, Al Abdallah Q, Robitaille R et al. Concentration of antifungal agents within host cell membranes: a new paradigm governing the efficacy of prophylaxis *Antimicrob. Agents Chemother*. 2011; 55: 5732–5739.
34. Dolton MJ, Ray JE, Marriott D, McLachlan AJ. Posaconazole exposure-response relationship: evaluating the utility of therapeutic drug monitoring. *Antimicrob Agents Chemother*. 2012; 56: 2806–2813.
35. Dolton MJ, Ray JE, Chen SCA, Ng K, Pont L, McLachlan AJ. Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. *Antimicrob Agents Chemother*. 2012; 56: 5503–5510.
36. Cornely OA, Ullmann AJ. Lack of evidence for exposure-response relationship in the use of posaconazole as prophylaxis against invasive fungal infections. *Clin Pharmacol Ther*. 2011; 89: 351–352.
37. Lewis RE, Kontoyiannis DP, Viale P, Sarpong EM. Using state transition models to explore how the prevalence of subtherapeutic posaconazole exposures impacts the clinical utility of therapeutic drug monitoring for posaconazole tablets and oral suspension. *Antimicrob Agents Chemother*. 2019; 63: 1–11.

APPENDIX 1

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