Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists

Neumayr, Andreas L C; Morizot, Gloria; Visser, Leo G; Lockwood, Diana N J; Beck, Bernhard R; Schneider, Stefan; Bellaud, Guillaume; Cordoliani, Florence; Foulet, Françoise; Laffitte, Emmanuel Alexis; Buffet, Pierre; Blum, Johannes A

How to cite

NEUMAYR, Andreas L C et al. Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists. In: Travel medicine and infectious disease, 2013, vol. 11, n° 6, p. 412–420. doi: 10.1016/j.tmaid.2013.05.003

This publication URL: https://archive-ouverte.unige.ch/unige:176162

Publication DOI: 10.1016/j.tmaid.2013.05.003

Travel Medicine and Infectious Disease (2013) xx, 1–9

Available online at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: www.elsevierhealth.com/journals/tmid

INVITED SUBMISSION

Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists

Andreas L.C. Neumayr [a,b,1], Gloria Morizot [c], Leo G. Visser [d,1], Diana N.J. Lockwood [e], Bernhard R. Beck [f,1], Stefan Schneider [g], Guillaume Bellaud [h], Florence Cordoliani [i], Françoise Foulet [j], Emmanuel A. Laffitte [k], Pierre Buffet [c,l], Johannes A. Blum [a,b,*,1]

[a] *Swiss Tropical and Public Health Institute, Socinstrasse 57, 4002 Basel, Switzerland*
[b] *University of Basel, Petersplatz 1, 4033 Basel, Switzerland*
[c] *Department of Parasitology and Mycology, Centre Médical Institut Pasteur, 25 — 28 Rue du Docteur Roux, 75724, Paris Cedex 15, France*
[d] *Leiden University Medical Centre, Department of Infectious Diseases C5P41, Albinusdreef 2, 2333 ZA Leiden, Netherlands*
[e] *London School of Hygiene & Tropical Medicine, Keppel St, London WC1E 7HT, United Kingdom*
[f] *Tropen- und Reisemedizin am Bellevue, Rämistrasse 3, 8001 Zürich, Switzerland*
[g] *Department of Rheumatology, Reha Rheinfelden, 4310 Rheinfelden, Switzerland*
[h] *Service de Dermatologie Centre Hospitalier Universitaire, 2 place St jacques, 25000 Besançon, France*
[i] *Department of Dermatology, Hôpital Saint-Louis, 1 Avenue Claude-Vellefaux, 75475, Paris Cedex 10, France*
[j] *Service de Parasitologie Mycologie, Hôpitaux Universitaires Henri-Mondor, Avenue du Mal de Lattre de Tassigny Créteil, France*
[k] *Clinic of Dermatology, Hôpitaux Universitaires de Genève, 1211 Genève 14, Switzerland*
[l] *Service de Parasitologie-Mycologie, Hôpital Pitié Salpêtrière, 47 Boulevard de l'hôpital, 75651, Paris Cedex 13, France & University Pierre et Marie Curie, Paris, France*

Received 27 March 2013; received in revised form 9 May 2013; accepted 13 May 2013

* Corresponding author. Swiss Tropical and Public Health Institute, Socinstr. 57, 4051 Basel, Switzerland. Tel.: +41 61 284 8111; fax: +41 61 284 8101.
E-mail addresses: andreas.neumayr@unibas.ch (A.L.C. Neumayr), johannes.blum@unibas.ch (J.A. Blum).
[1] TropNet — European Network for Tropical Medicine and Travel Health (www.tropnet.net).

1477-8939/$ - see front matter
http://dx.doi.org/10.1016/j.tmaid.2013.05.003

KEYWORDS
Cutaneous leishmaniasis;
TNF-alpha antagonists;
Rheumatology;
Treatment;
Immunosuppression

Summary Patients under immunosuppressive therapy with tumor necrosis factor alpha (TNF-α) antagonists are vulnerable to various opportunistic infections including leishmaniasis. We present a case series of 8 travellers developing cutaneous leishmaniasis whilst on TNF-α antagonist treatment and review the literature on aspects of cutaneous leishmaniasis developing in patients treated with TNF-α antagonists.

We make interim recommendations regarding the drug therapy used to maintain remission in travellers with rheumatoid disease travelling to leishmania prone areas. Despite having a medical condition requiring continued rheumatological review the interval to diagnosis appears not to be reduced compared to that described in non-rheumatoid patients. Rheumatologists and family doctors should be aware of the need for post-travel surveillance for leishmaniasis in rheumatoid patients on TNF-alpha antagonist treatment.

Introduction

In 1993 the introduction of tumor necrosis factor (TNF-α) antagonists added a new drug group to the treatment options for rheumatoid arthritis and other auto-immune mediated inflammatory diseases. While the successful therapy of these frequently incapacitating and immobilising diseases dramatically improved the lives of many patients, the treatment-associated impairment of cellular immunity puts these patients at risk for opportunistic infections like leishmaniasis. Next to the rising numbers of immunosuppressed residents within leishmania endemic regions the successful treatment of previously incapacitating diseases has led to an increase in the number of such patients travelling to leishmania endemic regions. In the recent years, clinical centres specialised in the treatment of leishmaniasis have diagnosed cutaneous leishmaniasis (CL) infections in rheumatoid patients (i.e. rheumatoid arthritis, ankylosing spondylitis, psoriasis arthritis) treated with TNF-α antagonists. In this paper we summarise the experiences of the European LeishMan working group regarding clinical aspects and management of CL in rheumatoid patients treated with TNF-α antagonists and review the literature on similar cases.

Material and methods

The LeishMan (**Leish**maniasis **Man**agement) working group was used to collect CL patients under treatment with TNF-α antagonists. The LeishMan network consists of 12 institutions in 7 European countries and aims on harmonising the diagnostic and therapeutic guidelines for cutaneous leishmaniasis (CL) and mucosal leishmaniasis (ML) infections in Europe (www.leishman.eu).

We also performed a PubMed (MEDLINE) literature search using the key words 'TNF-α antagonist', 'immunosuppression', 'cutaneous leishmaniasis', 'infliximab', 'adalimumab', 'etarnercept', 'golimumab', and 'certolizumab', including articles in English, French, German, and Spanish and screened the references of the collected publications for publications with similar content.

Results

We collected 8 cases developing cutaneous leishmaniasis whilst on TNF-α antagonist treatment within the LeishMan network. All cases were travellers residing in non-endemic regions who acquired the infection while travelling to endemic regions (nos. 1–8; Tables 1 and 2). The literature review identified 8 additional cases developing CL whilst receiving TNF-α antagonist treatment (Case nos. 9–16; Tables 1 and 2). The 16 cases are summarised in Tables 1 and 2.

Information on the methodology of species determination was only available for the cases diagnosed in-house at the Swiss Tropical and Public Health Institute (Case nos. 4–7). In these cases DNA extraction and PCR amplification of the polymorphic miniexon marker was performed as described previously [1,2]. For species determination PCR products were restriction digested with four to six restriction enzymes depending on the leishmania species complex identified. Restriction fragments were separated by polyacrylamide gel electrophoresis and patterns of restriction fragments were compared to those from reference strains [1,2].

An approximate incubation period was calculable in 8 cases, where the patients spent only a limited period of time in endemic regions (i.e. tourism); the incubation periods varied between ~1 and ~15 months (median ~7.5 months). In 8 cases the incubation period was not determinable. Interestingly 2 patients were migrants who had left their leishmania endemic home countries 5 and 10 years before the onset of symptoms and neither had visited leishmania endemic regions since (Case nos. 10 & 11).

The initial presentation was CL in 15 patients and ML in one patient.

Information on the period between onset of symptoms and definitive diagnosis of leishmaniasis was available for 11 patients, and ranged from ≤1 month to ~7 years (median ~4 months).

Regarding the number of CL skin lesions: 6 patients had 1 lesion, 2 patients had 2 lesions, 3 patients had 3 lesions, and 3 patients presented with multiple lesions. Among the patients with multiple lesions 1 had multiple lesions on both auricles, 1 had multiple facial lesions, and 1 had disseminated CL with more than 100 papulo-nodular skin lesions (Fig. 1). In 2 cases the exact number of skin lesions was not specified.

After the diagnosis of leishmaniasis was established, TNF-α antagonist therapy was discontinued in 7 cases, temporarily discontinued in 3 cases, and continued in 5 cases. In 1 case no information was available on the therapy of the underlying disease after diagnosis.

In 1 case no data on treatment outcome was available. All other cases showed clinical cure following initial

Please cite this article in press as: Neumayr ALC, et al., Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists, Travel Medicine and Infectious Disease (2013), http://dx.doi.org/10.1016/j.tmaid.2013.05.003

Table 1 Baseline data on geographic background of infection, leishmania species, clinical manifestation(s), and timeframe.

Pat. no.	Age Sex	Underlying disease (diagnosed)	Immunosuppressive/ modulating drug(s)	Most likely place (Date) of infection	Species	Number of skin lesions	Description & max. size of lesion(s)	Onset of symptoms/ appearance of lesion(s)	Diagnosis established	Reference
1	51 F	Ankylosing spondylitis (2004)	Adalimumab 40 mg/14d (06/2006—02/2008)	Algeria (08/2007)	*L. infantum*	2	Ulcer, Ø 50 mm	02/2008	08/2008	LeishMan working group data
2	51 M	Ankylosing spondylitis (1975)	Adalimumab from 05/2010 (initially 1×/14d, later 1×/21d)	Italy (05/2011)	*L. infantum*	2	Nodule, Ø 20 mm	06/2011	09/2011	
3	41 M	Psoriatic arthritis (2005)	Methotrexate (2005—2008), leflunomide & salazopyrine (2007—2009), infliximab 3 mg/kg/8 weeks (starting 01/2010)	Argentina (04/2010)	No data	1	Ulcer, Ø 60 mm	10/2010	10/2011	
4	47 M	Rheumatoid arthritis (2006)	Prednison 7.5 mg/d (cont.), methotrexat 15 mg/week (02/2007—09/2008), leflunomid 20 mg/d (02/2008—04/2009), etanercept (06/2007—02/2008), infliximab 5 mg/kg/6 weeks (02/2008- 05/2008), infliximab 5 mg/kg/4 weeks (05/2008—10/2008)	Egypt? (03/2007)	*L. infantum*	Multiple disseminated lesions (face, body, arms)	Nodules (see Fig. 1)	06/2008	10/2008	
5	50 M	Ankylosing spondylitis	Etanercept 50 mg/week (06/2010—12/2011)	Egypt? (12/2010—01/2011)	*L. aethiopica*	Multiple lesions at both auricles (ears)	Crusted lesions	04/2011	06/2011	
6	59 M	Psoriatic arthritis	Methotrexate 7.5 mg/week, infliximab 400 mg/8 weeks	South France, Mallorca (no data)	*L. infantum*	3	Erythrosquamous lesion, Ø 40 mm	No data	2 Months after appearance of lesions	
7	53 M	Psoriatic arthritis	Efalizumab (until 1.5 years before CL diagnosis), then adalimumab 40 mg/2 weeks	Mallorca (every year since 15 years)	*L. infantum*	1	Granulomatous ulcerative nasal mucosa (ML)	No data	8 Months after appearance of lesion	

(*continued on next page*)

Please cite this article in press as: Neumayr ALC, et al., Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists, Travel Medicine and Infectious Disease (2013), http://dx.doi.org/10.1016/j.tmaid.2013.05.003

Table 1 (*continued*)

Pat. no.	Age Sex	Underlying disease (diagnosed)	Immunosuppressive/ modulating drug(s)	Most likely place (Date) of infection	Species	Number of skin lesions	Description & max. size of lesion(s)	Onset of symptoms/ appearance of lesion(s)	Diagnosis established	Reference
8	56 M	Rheumatoid arthritis (2001)	Prednisone, methotrexate 10 mg-15/week (2002–2011), + adalimumab 40 mg/2 weeks (2005–02/2011), 2 doses of rituximab (04/2011–05/2011)	Italy (2001), Spain (2002), Greece (every year since 14 years)	*L. infantum*	Nasal cutaneous lesion (no data on number of lesions)	Swelling, erythema, crusting	2004	07/2011	
9	31 M	Ankylosing spondylitis	Infliximab	Mallorca (9 months prior to skin lesion)	*L. infantum*	1	No data	9 months after exposure	Within 1 month after onset of symptoms	Mueller et al., 2009 [20]
10	42 F	Rheumatoid arthritis	Prednisone (low dose 2000–2004), after 2004: methotrexate, adalimumab	Brazil (migrant, leaving Brazil 1999)	*L. chagasi*	1	Ulcer, 40 × 25 mm	11/2004, 2–3 months after treatment with adalimumab	06/2007	Franklin et al., 2009 [21]
11	50 M	Ankylosing spondylitis	Prednisone, infliximab 5 mg/kg every 6 weeks	Algeria (migrant, no travelling to endemic region >10 years)	*L. infantum*	3	Ø 10–20 mm	After 9th infusion of infliximab, 10 years after leaving Algeria	No data	Hakimi et al., 2010 [22]
12	56 F	Rheumatoid arthritis (1992)	Methotrexate 15 mg/week and prednisone 3.75 mg/d until 10/2000, 10/2000 addition of infliximab, 05/2004 replacement of infliximab by adalimumab	Northeastern Spain (resident)	No data	Localized CL on right leg (no data on number of lesions)	No data	No data	07/2004	Baltà-Cruz et al., 2009 [23]
13	38 M	Rheumatoid arthritis	Infliximab, methotrexate, prednisone	Eritrea (migrant)	*L. aethiopica*	1	60 × 50 mm	1 year after exposure, 2 weeks after infliximab	No data	Zanger et al., 2011 [24]
14	55 M	Ankylosing spondylitis (1998)	Infliximab 3 mg/kg methotrexate 10 mg weekly	Greece (resident)	No data	Multiple facial lesions (no data on number of lesions)	Encrusted vesicular lesions	No data	No data	Xynos et al., 2009 [25]

Please cite this article in press as: Neumayr ALC, et al., Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists, Travel Medicine and Infectious Disease (2013), http://dx.doi.org/10.1016/j.tmaid.2013.05.003

15	51 F	Ankylosing spondylitis (2004)	Adalimumab 40 mg/2 weeks (6/2006–6/2008) ± (?) methotrexate	Algeria (migrant)	*L. infantum*	3	1 ulcer, Ø 50 mm, 2 nodular lesions	02/2008	06/2008	Schneider et al., 2009 [26]
16	36 F	Ankylosing spondylitis (2004)	Adalimumab 40 mg/3 weeks and methotrexate 10 mg/week (since 1 year prior to CL diagnosis)	Brazil (resident)	No data[a]	1	Ulcer, Ø 15 mm	No data	No data	Gomes et al., 2012 [27]

[a] Diagnosis based on epidemiology, clinical picture, positive Montenegro test, and response to treatment (no detection of leishmania parasites in direct smear; leishmania culture negative; PCR not performed).

Table 2 Therapy and treatment outcome.

Pat. no.	Treatment	Treatment outcome	Immunosuppressive/ modulating drug(s) after diagnosis	Follow-up/relapse	Reference
1	Liposomal amphotericin B: cumulative dose 27 mg/kg	Clinical cure	Discontinuation of adalimumab	No relapse; loss to follow-up 1 month after treatment (last follow-up 09/2008)	LeishMan working group data
2	Intra-lesional meglumine antimoniate (Glucantime): 5 injections	Clinical cure	Discontinuation of adalimumab	No relapse during follow-up for 4 months (last follow-up 01/2012); currently under surveillance	
3	Cryotherapy + intra-lesional meglumine antimoniate (Glucantime): 3 injections	Clinical cure	Continuation of infliximab	No relapse during follow-up for 7 months (last follow-up 05/2012); currently under surveillance	
4	Meglumine antimoniate 20 mg/kg i.m. × 28d	Clinical cure	Continuation of infliximab 3 mg/kg/8 weeks, methotrexate 7.5 mg/week, prednisone 5 mg/d	No relapse during follow-up for 44 months (last follow-up 06/2012); currently under surveillance	
5	Miltefosine 50 mg TID × 28d	Clinical cure	Continuation of etanercept 25 mg/week	No relapse during follow-up for 7 months (last follow-up 01/2012); currently under surveillance	

(*continued on next page*)

Table 2 (*continued*)

Pat. no.	Treatment	Treatment outcome	Immunosuppressive/ modulating drug(s) after diagnosis	Follow-up/relapse	Reference
6	Miltefosine 50 mg TID × 28d	Clinical cure	Continuation of ant-TNF therapy, but unclear combination/sequential therapy of etanercept, methotrexate & adalimumab	No relapse for ?[a] months (last follow-up 01/2012); currently under surveillance	
7	Miltefosine 50 mg TID × 28d	Clinical cure	Discontinuation of adalimumab; methotrexate 15 mg/week, leflunomide, ustekinumab	No relapse for ?[a] months (last follow-up 01/2012); currently under surveillance	
8	Sodium stibogluconate 20 mg/kg × 28d	Clinical cure	Discontinuation of prednisone, methotrexate, (adalimumab already discontinued prior to diagnosis)	No relapse for 10 months; currently under surveillance (last follow-up 05/2012)	
9	Miltefosine 50 mg BID × 6 weeks	Clinical cure	Continuation of infliximab, also after relapse	Relapse after ~1 year: treatment with 2 injections of intra-lesional sodium stibogluconate → clinical cure after 5 months; no relapse during 2 years follow-up	Mueller et al., 2009 [20]
10	Liposomal amphotericin B	Clinical cure	No data	No data	Franklin et al., 2009 [21]
11	Intra-lesional meglumine antimoniate weekly × 6 weeks	Clinical cure	Discontinuation of infliximab	No relapse in the following 3 years	Hakimi et al., 2010 [22]
12	Intra-lesional meglumine antimoniate and surgical excision	No data	MTX, prednisone and adalimumab were maintained until 07/2006 and temporarily discontinued during treatment of ML	Relapse after ~2 years (07/2006): ML of the upper lip, hard palate and septum: administration of liposomal amphotericin B (3 mg/kg/d), which was — due to adverse events — changed to meglumine antimoniate 20 mg/kg i.m. for 13d; no relapse during 1 year follow-up	Baltà-Cruz et al., 2009 [23]
13	Liposomal amphotericin B: cumulative dose 60 mg/kg (200 mg/d × 22d)	Clinical cure	Temporary discontinuation of TNF-antagonist treatment: discontinuation	No relapse within 1 year	Zanger et al., 2011 [24]

			of infliximab, restart on etanercept, methotrexate, & prednisone 1 month after end of treatment		
14	Liposomal amphotericin B: cumulative dose 21 mg/kg	Clinical cure	Temporary discontinuation of infliximab	Restart of etanercept 18 months later; no relapse in the following 2 years	Xynos et al., 2009 [25]
15	Liposomal amphotericin B: cumulative dose 21 mg/kg	Clinical cure	Discontinuation of adalimumab	No data	Schneider et al., 2009 [26]
16	Meglumine antimoniate (Glucantime): dose not stated	Clinical cure	Discontinuation of adalimumab	No data	Gomes et al., 2012 [27]

[a] Data on time interval between treatment and follow-up is missing.

treatment. Two patients showed relapse after ~1 year and ~2 years. Both relapse patients showed clinical cure to re-treatment and no more relapses were observed during the 1 year and 2 years follow-up period (Case nos. 9 & 12).

Discussion

To our knowledge we present the largest ever published cases series of CL infections in patients treated with TNF-α antagonists. Even though the heterogeneity of the cases (different immunosuppressive therapies with different drug- and dosage regimens, leading to very individual degrees of immunosuppression), the lack of data on methodology of leishmania species determination, and the different anti-leishmanial treatment regimens do not allow deeper data analysis, the collected case descriptions provide some interesting insights.

The incubation period of CL in patients treated with TNF-alpha antagonists appears to be relatively long (median 7.5 months [1–15 months]) compared to non-immunosuppressed patients. In a case series of 39 French tourists the median incubation period of old world CL was 28 days (5–150 days) [3], but comparing data between case series is difficult as the distribution of the involved leishmania species can distort the picture.

CL development many years after infection (as in Case nos. 10 & 11) has been observed in patients with immunosuppression after organ transplantation [4]. Persistence of leishmania has been documented in scar tissue [5] and blood [6] of successfully treated patients, illustrating that there is no sterile cure of leishmaniasis and that persisting leishmania may recrudesce following immunosuppression.

Despite the increased risk for opportunistic infections in immunosuppressive patients, the diagnosis of leishmaniasis is not established faster in these patients than in healthy travellers. In two studies on CL in travellers the median time interval between onset of cutaneous lesions and diagnosis of CL was 4 months (19 days–24 months) and 95 days (3 days–150 days) [3,7]. In our case series the median time interval between onset of cutaneous lesions and diagnosis of CL was identical: 4 months (≤1 month–7 years).

Surprisingly, the number of CL skin lesions in patients receiving TNF-α antagonist therapy and in non-immunosuppressed CL patients is similar: in both groups most patients present with 1–3 lesions [7]. Disseminated CL remains a rare condition: Most published cases are HIV co-infected patients [8] and one case report exists on disseminated CL in an immunosuppressed kidney transplant recipient [9]. Interestingly the cutaneous lesions of the patient with disseminated CL (Case no. 4) appeared after the dosage interval of infliximab (5 mg/kg) had been shortened from 6 to 4 weeks.

We did not find any differences in morphology and size of the lesions when comparing data from the CL patients under TNF-α antagonist therapy and published data from non-immunosuppressed individuals [10].

As all reviewed leishmaniasis patients under TNF-α antagonist therapy were treated successfully, we conclude that these patients can be treated by using the usual recommendations and guidelines [11–13].

Please cite this article in press as: Neumayr ALC, et al., Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists, Travel Medicine and Infectious Disease (2013), http://dx.doi.org/10.1016/j.tmaid.2013.05.003

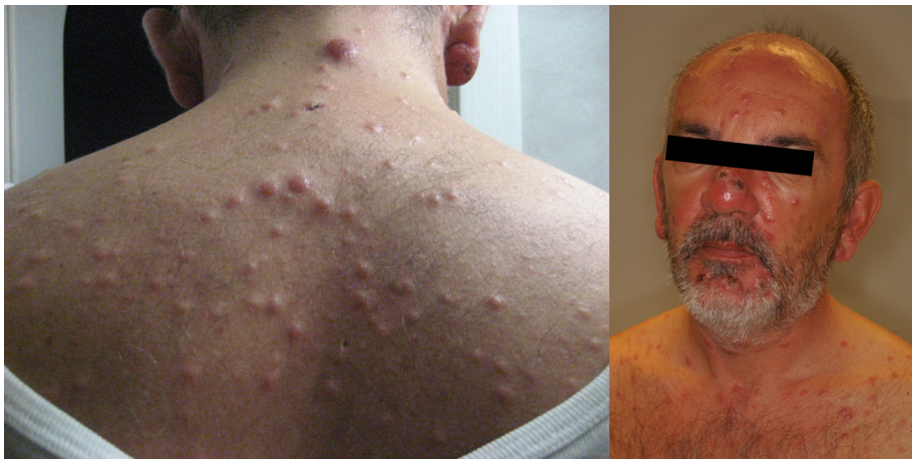

Figure 1 Case no. 4: disseminated cutaneous leishmaniasis.

Currently there are not enough data to conclude whether TNF-α antagonist therapy should be discontinued during or after anti-leishmanial treatment. The risk of progression of the underlying rheumatologic disease has to be balanced against the risk of leishmaniasis — especially the risk of developing mucosal and/or visceral leishmaniasis. Although no data from prospective studies are currently available, we recommend that TNF-α antagonist therapy is discontinued during anti-leishmanial treatment. After complete resolution of the skin lesions TNF-α antagonist therapy might be restarted with the smallest needed dosage under close clinical monitoring. In the patient with disseminated CL (Case no. 4) it was possible to control the symptoms of rheumatoid arthritis with a lower dose of infliximab (3 mg/kg/8 weeks) without relapse of leishmaniasis.

Recently Zanger et al. evaluated the risk of opportunistic leishmaniasis for the two different types of TNF-α antagonists (the anti-TNF monoclonal antibodies and the soluble TNF-receptor construct etanercept) in the European region and found a 8-fold increased odds of opportunistic leishmaniasis in patients treated with the monoclonal antibodies infliximab and adalimumab as opposed to patients treated with etanercept. The authors also provide a summary of possible explanations by reviewing the differences in subcellular interaction of the two types of TNF-α antagonists [14]. This observation suggests that until evidence from prospective research is available, etanercept should be used rather than anti-TNF monoclonal antibodies in patients living in or travelling to leishmania endemic regions.

Case reports have been published on patients with tuberculosis and pulmonary cryptococcosis where discontinuation of TNF-α antagonist therapy led to paradoxical clinical reactions attributed to immune reconstitution [15]. While leishmania-related immune reconstitution inflammation syndrome (IRIS) has been observed in HIV-patients [16,17], leishmania-related IRIS has not been reported after discontinuation of TNF-α antagonist therapy.

In case of relapsing CL anti-leishmanial prophylactic (suppressive) treatment with pentamidine (successfully used in patients with immunosuppression and relapsing VL [18]), amphotericin B (successfully used in HIV positive patients with CD4 counts below 200 cells/mm [3] and VL [19]) or meglumine antimoniate might be a feasible option. Although data on this approach are currently lacking, it might especially be worth to consider this option in cases where the continuation of immunosuppressive therapy is inevitable and the leishmania species may cause visceral disease.

Concerning the complex choice of second-line treatment in case of relapse, the existing national recommendations and guidelines are not uniform and no treatment consensus is currently available, neither for immunocompetent nor for immunosuppressed individuals. In case of relapse most clinicians opt for a second-line treatment different from first-line therapy.

We are convinced that the LeishMan working group will not only provide the ideal platform to harmonize the diagnostic and therapeutic guidelines for CL and ML in Europe, but also help to gain more experience on how to best manage this currently rare and possibly emerging disease in immunocompromised travellers and residents of leishmania endemic regions.

Funding

None.

Conflict of interest

The authors state that they have no conflicts of interest.

References

[1] Marfurt J, Niederwieser I, Makia D, Beck HP, Felger I. Diagnostic genotyping of Old and New World Leishmania species by PCR-RFLP. Diagn Microbiol Infect Dis 2003;46:115—24.

[2] Marfurt J, Nasereddin A, Niederwieser I, Jaffe CL, Beck HP, Felger I. Identification and differentiation of Leishmania species in clinical samples by PCR amplification of the miniexon sequence and subsequent restriction fragment length polymorphism analysis. J Clin Microbiol 2003;417:3147—53.

Please cite this article in press as: Neumayr ALC, et al., Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists, Travel Medicine and Infectious Disease (2013), http://dx.doi.org/10.1016/j.tmaid.2013.05.003

[3] El Hajj L, Thellier M, Carriere J, Bricaire F, Danis M, Caumes E. Localized cutaneous leishmaniasis imported into Paris: a review of 39 cases. Int J Dermatol 2004;43:120–5.
[4] Antinori S, Cascio A, Parravicini C, Bianchi R, Corbellino M. Leishmaniasis among organ transplant recipients. Lancet Infect Dis 2008;8:191–9.
[5] Schubach A, Haddad F, Oliveira-Neto MP, Degrave W, Pirmez C, Grimaldi Jr G, et al. Detection of Leishmania DNA by polymerase chain reaction in scars of treated human patients. J Infect Dis 1998;178:911–4.
[6] de Oliveira CP, Junger J, do Espirito Santo Silva Pires Mattos M, Oliveira-Neto MP, Fernandes O, et al. Haematogenous dissemination of Leishmania (Viannia) braziliensis in human American tegumentary leishmaniasis. Trans R Soc Trop Med Hyg 2006;100:1112–7.
[7] Harms G, Schönian G, Feldmeier H. Leishmaniasis in Germany. Emerg Infect Dis 2003;9:872–5.
[8] Chaudhary RG, Bilimoria FE, Katare SK. Diffuse cutaneous leishmaniasis: co-infection with human immunodeficiency virus (HIV). Indian J Dermatol Venereol Leprol 2008;74:641–3.
[9] Venencie PY, Bourée P, Hiesse C, Vieillefond A, Lantz O, Doukan S, et al. Disseminated cutaneous leishmaniasis in a case of an immunodepressed woman. Ann Dermatol Venereol 1993;120:461–3.
[10] Harms G, Scherbaum H, Reiter-Owona I, Stich A, Richter J. Treatment of imported New World cutaneous leishmaniasis in Germany. Int J Dermatology 2011;50:1336–42.
[11] Blum JA, Lockwood DNJ, Visser L, Harms G, Baileye MS, Caumes E, et al. Local or systemic treatment for New World cutaneous leishmaniasis? Re-evaluating the evidence for the risk of mucosal leishmaniasis. International Health 2012;4:153–63.
[12] Blum JA, Hatz CF. Treatment of cutaneous leishmaniasis in travelers. J Travel Med 2009;16:123–31.
[13] Buffet PA, Rosenthal E, Gangneux JP, Lightburne E, Couppié P, Morizot G, et al. Therapy of leishmaniasis in France: consensus on proposed guidelines. Presse Med 2011;40:173–84.
[14] Zanger P, Kötter I, Kremsner PG, Gabrysch S. Tumor necrosis factor alpha antagonist drugs and leishmaniasis in Europe. Clin Microbiol Infect 2012;18:670–6.
[15] Moureau C, Pothen L, Wilmes D, Yombi JC, Coche E, Hainaut P. Paradoxical response to tuberculosis treatment in a patient receiving tumor necrosis factor-alpha antagonist. Am J Med 2012;125:e9–10.
[16] Posada-Vergara MP, Lindoso JA, Tolezano JE, Pereira-Chioccola VL, Silva MV, Goto H. Tegumentary leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome in 2 patients with AIDS. J Infect Dis 2005;192:1819–22.
[17] Chrusciak-Talhari A, Ribeiro-Rodrigues R, Talhari C, Silva Jr RM, Ferreira LC, Botileiro SF, et al. Tegumentary leishmaniasis as the cause of immune reconstitution inflammatory syndrome in a patient co-infected with human immunodeficiency virus and Leishmania guyanensis. Am J Trop Med Hyg 2009;81:559–64.
[18] Patel TA, Lockwood DN. Pentamidine as secondary prophylaxis for visceral leishmaniasis in the immunocompromised host: report of four cases. Trop Med Int Health 2009;14:1064–7.
[19] Molina I, Falcσ V, Crespo M, Riera C, Ribera E, Curran A, et al. Efficacy of liposomal amphotericin B for secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. J Antimicrob Chemother 2007;60:837–42.
[20] Mueller MC, Fleischmann E, Grunke M, Schewe S, Bogner JR, Löscher T. Relapsing cutaneous leishmaniasis in a patient with ankylosing spondylitis treated with infliximab. Am J Trop Med Hyg 2009;81:52–4.
[21] Franklin G, Greenspan J, Chen S. Anti-tumor necrosis factor-alpha therapy provokes latent leishmaniasis in a patient with rheumatoid arthritis. Ann Clin Lab Sci 2009;39:192–5.
[22] Hakimi S, Rivière S, Del Giudice P, Dereure J, Le Quellec A. Localized cutaneous leishmaniasis due to leishmania infantum in a patient treated with infliximab. Dermatology 2010;220:63–5.
[23] Baltà-Cruz S, Alsina-Glbert M, Mozos-Rocafort A, Cervera C, Colomo-Saperas L, Del Río A, et al. Pseudolymphomatoid cutaneous leishmaniasis in a patient treated with adalimumab for rheumatoid arthritis. Acta Derm Venereol 2009;89:432–3.
[24] Zanger P, Kötter I, Raible A, Gelanew T, Schönian G, Kremsner PG. Case report: successful tratment of cutaneous leishmaniasis caused by Leishmania aethiopica with liposomale amphotericin B in an immunocompromised traveler returning from Eritrea. Am J Trop Med Hyg 2011;84:692–4.
[25] Xynos ID, Tektonidou MG, Pikazis D, Sipsas NV. Leishmaniasis, autoimmune rheumatic disease, and anti-tumor necrosis factor therapy, Europe. Emerg Infect Dis 2009;15:956–9.
[26] Schneider P, Bouaziz JD, Foulet F, Duong TA, Allanore LV, Bagot M. Multifocal cutaneous leishmaniasis due to Leishmania infantum under adalimumab therapy. Ann Dermatol Venereol 2009;136:815–6.
[27] Gomes KW, Benevides AN, Vieira FJ, Burlamaqui MP, Vieira Mde A, Fontenelle LM. Cutaneous leishmaniasis in a patient with ankylosing spondylitis using adalimumab. Rev Bras Reumatol 2012;52:447–52.

Please cite this article in press as: Neumayr ALC, et al., Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists, Travel Medicine and Infectious Disease (2013), http://dx.doi.org/10.1016/j.tmaid.2013.05.003