# German S3-Guideline on the treatment of Psoriasis vulgaris, adapted from EuroGuiDerm - Part 2: Treatment monitoring and specific clinical or comorbid situations

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Guideline

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# German S3-Guideline on the treatment of Psoriasis vulgaris, adapted from EuroGuiDerm – Part 2: Treatment monitoring and specific clinical or comorbid situations

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**Table 1** Decision grid (I) for the "conventional" treatment options and the expert assessment of their suitability in specific treatment circumstances.

| Therapy / Specific circumstances | Conventional systemic agents | | | |
|---|---|---|---|---|
| | Acitretin | Ciclosporin | Fumarates | Methotrexate |
| Psoriatic arthritis | | | | ↑↑ peripheral active joint involvement |
| Chronic inflammatory bowel disease: Crohn's disease | ↑ especially cases with mild paradoxical psoriasis | | | ↑ 2nd choice if oral treatment preferred |
| Chronic inflammatory bowel disease: ulcerative colitis | ↑ especially cases with mild paradoxical psoriasis | ↑ 2nd choice if oral treatment preferred | | |
| Diabetes mellitus/ metabolic syndrome | | ↓ | | ↓ |
| Dyslipidemia | ↓ | ↓ | | |
| Advanced heart failure | ↑ | ↓ | | ↑ |
| Heart disease: ischemic heart disease | ↓ | ↓ | | ↑ |
| Latent/treated TB | ↑ | | ↑ | |
| Pregnancy | ↓↓ | | ↓ | ↓↓ |

| Symbols | Implications |
|---|---|
| ↑ | We believe that all or almost all informed people would make a choice in favour of using this intervention. Clinicians will not have to spend as much time on the process of decision-making with the patient and may devote that time instead to overcoming barriers to implementation and adherence. In most clinical situations, the recommendation can be adopted as a policy. |
| ↑ | We believe that most informed people would make a choice in favour of using this intervention, but a substantial number would not. Clinicians and other health care providers will need to devote more time to the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making will require substantial debate. |
| | See background text and specific recommendations. |
| ↓ | We believe that most informed people would make a choice against using this intervention, but a substantial number would not. |
| ↓↓ | We believe that all or almost all informed people would make a choice against using this intervention. This recommendation can be adopted as a policy in most clinical situations. |

For chapters 1 (Notes on use/Disclaimer), 3 (Funding), 4 (Scope and purpose of this guideline), 5 (Population and health questions covered by the guideline) and 6 (Targeted users of this guideline), see long version of the guideline.

 

Table 2 Decision grid (II) for treatment options with biologics and the expert assessment of their suitability in specific treatment circumstances.

| Therapy / Specific circumstances | Small molecules | TNF inhibitors | | | | Anti-IL12/23p40 | Anti-IL17 | | | Anti-IL23 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apremilast | Etanercept | Infliximab | Adalimumab | Certolizumab | Ustekinumab | Secukinumab | Ixekizumab | Brodalumab | Guselkumab | Tildrakizumab | Risankizumab |
| Psoriatic arthritis | | ↑↑ if non-responder to MTX | | | | | | | | | | |
| Chronic inflammatory bowel disease: Crohn's disease | | | ↑↑ 1st choice | | | | ↓ | | | ↑ 2nd choice if anti-TNF alpha not suitable | | |
| Chronic inflammatory bowel disease: ulcerative colitis | ↑ 2nd choice oral treatment | | ↑↑ 1st choice | | | ↑↑ 1st choice | ↓ | | | ↑ 2nd choice if anti-TNF alpha not suitable | | |
| Diabetes mellitus/ metabolic syndrome | | | | | | | | | | | | |
| Dyslipidemia | | | | | | | | | | | | |
| Advanced heart failure | ↑ | ↓↓ | | | | | ↑ | | | | | |
| Heart disease:ischemic heart disease | | ↑ | | | | | | | | | | |
| Latent / treated TB | ↑ | ↓↓ | | | | | ↑ | | | ↑ | | |
| Pregnancy | ↓ | | | | ↑ | | | | | | | |

## Accompanying documents

- Long version of the guideline
- Part 1: Treatment goals and treatment recommendations
- Supplemental material: Topical therapy, phototherapy, additional therapeutic options, interfaces between different providers and sectors of care (in German only)
- Guideline Development Report and Evidence Report
- PowerPoint slides to aid guideline implementation

All documents are available in an up-to-date version on the following website: https://debm.charite.de

## Guideline text and recommendations

### Guidance for specific clinical and comorbid situations

**Psoriatic arthritis: How should psoriasis patients with concomitant psoriatic arthritis be managed?**

This chapter is based on the related chapter in previous versions of this guideline [1, 2]. An existing systematic review and meta-analysis was updated, details of which can be found in the Guideline Development Report.

*Recommendations [3–6]*

| | | |
|---|---|---|
| We *recommend* interdisciplinary cooperation with a rheumatologist for the confirmation of the diagnosis of psoriatic arthritis and the selection of a suitable treatment whenever needed. | ↑↑ | Strong consensus, consensus-based |

Treatments are usually categorized as non-steroidal anti-inflammatory drug (NSAIDs)/COX-2 inhibitors (e.g., diclofenac, etoricoxib), conventional synthetic disease modifying anti rheumatic drugs (csDMARDs; e.g., MTX), targeted synthetic disease modifying anti rheumatic drugs (tsDMARDS; e.g., apremilast) and biological disease modifying anti rheumatic drugs (bDMARDs; e.g., TNF-antagonists).

Head-to-head trials allowing direct comparison between the different groups or between the individual drugs are extremely rare. Indirect comparisons, e.g., network meta-analyses, are limited by the low number of trials for psoriatic arthritis. See Table 3 for an overview of randomized controlled trial (RCT) data on psoriatic arthritis.

*Non-steroidal anti-inflammatory drugs (NSAIDs)*

The role of NSAIDs is usually in the relief of symptoms of psoriatic arthritis for patients with mild and non-erosive articular as well as para-articular, entheseal involvement. Treatment of NSAIDs should be limited to the lowest required dosage for the shortest period as needed [8].

*Conventional synthetic DMARDs (e.g., MTX)*

| | | |
|---|---|---|
| We *recommend* starting a conventional synthetic DMARD (MTX) early to prevent progression of disease and erosive destruction of joints for patients with moderate-to-severe psoriasis and peripheral active joint involvement (PsA) despite the usage of NSAIDs/COX-2 inhibitors, or glucocorticoid site injections if applicable and/or potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, entheseal and extra-articular musculoskeletal manifestations. | ↑↑ | Strong consensus, evidence- and consensus-based (see Table 3) |

Methotrexate is recommended, taking the label, the efficacy on skin and peripheral joints, the safety profile and the available long-term experience in the treatment of rheumatic joint disorders into to account [8].

| | | |
|---|---|---|
| We *do not recommend* synthetic monotherapy DMARDs (MTX) for the treatment of axial involvement or enthesitis, as they appear to be not effective in these patients. | ↓↓ | Strong consensus, consensus-based |

*Biological DMARDs*

| | | |
|---|---|---|
| For inadequately responding patients after at least one synthetic DMARD, we *recommend* using biological DMARDs as monotherapy or in combination with synthetic DMARDs in patients with moderate-to-severe psoriasis with active joint involvement (PsA). | ↑↑ | Strong consensus, evidence- and consensus-based (see Table 3) |
| For the selection of a bDMARD for patients with moderate-to-severe psoriasis of the skin and active joint involvement (PsA), we *recommend* taking aspects of efficacy with regard to skin and the joints, comorbidity, practicability and safety into account. | ↑↑ | Strong consensus, consensus-based |

Previously, guidelines have given a preference to TNF alpha antagonists over other bDMARDs. In the guideline group's view, a preference for inhibitors of TNF treatments for PsA is no longer mandatory, since ustekinumab (enthesitis) and the IL-17A antibody treatments might be equally effective; however more data are needed for its real-life long-term efficacy, safety and co-medication.

The treatment with a biological DMARD can be performed in monotherapy or in combination with a conventional synthetic DMARD.

*Other treatment options*

Considering the evidence on skin and joint involvement and the experience of the expert group, apremilast is primarily suggested for patients with moderate-to-severe psoriasis and concomitant psoriatic arthritis with an inadequate response to at least one csDMARD, in whom biological treatments are not appropriate.

 

Table 3 Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al. [7] updated, see Guideline Development Report).

| | Patients achieving ACR20 | | | Patients with at least one adverse event | | |
|---|---|---|---|---|---|---|
| | RR | 95 % CI | Quality of the Evidence (GRADE) | RR | 95 % CI | Quality of the Evidence (GRADE) |
| *Head-to-head comparisons* | | | | | | |
| ETA 50 mg + MTX vs. MTX 20 mg QW | 1.28 | 1.11 to 1.48 | LOW | 1.01 | 0.92 to 1.11 | MODERATE |
| INF 5 mg/kg W 0, 2, 6, 14 + MTX vs. MTX 15 mg QW | 1.40 | 1.07 to 1.84 | VERY LOW | 1.65 | 1.08 to 2.52 | VERY LOW |
| IXE 80 mg Q2W vs. ADA 40 mg Q2W | 1.08 | 0.86 to 1.36 | LOW | 1.02 | 0.83 to 1.25 | MODERATE |
| IXE 80 mg Q4W vs. ADA 40 mg Q2W | 0.96 | 0.86 to 1.06 | LOW | 1.14 | 1.01 to 1.28 | VERY LOW |
| *Placebo comparisons* | | | | | | |
| ADA 40 mg EOW vs. PBO | 3.35 | 2.24 to 4.99 | MODERATE | 0.67 | 0.50 to 0.89 | VERY LOW |
| APR 30 mg BID vs. PBO | 1.94 | 1.59 to 2.38 | MODERATE | 1.24 | 1.12 to 1.36 | LOW |
| APR 20 mg BID vs. PBO | 1.86 | 1.49 to 2.31 | MODERATE | 1.27 | 1.15 to1.41 | LOW |
| CZP 400 mg Q4W vs. PBO | 2.36 | 1.68 to 3.31 | MODERATE | 1.05 | 0.90 to 1.23 | MODERATE |
| CZP 200 mg Q2W vs. PBO | 2.71 | 1.95 to 3.76 | MODERATE | 1.01 | 0.86 to 1.19 | MODERATE |
| ETA 25 mg BIW vs. PBO | 4.05 | 2.56 to 6.40 | LOW | n.d. | | |
| INF 5 mg/kg W 0, 2, 6, 14 vs. PBO | 4.38 | 2.24 to 8.56 | MODERATE | 1.13 | 0.87 to 1.47 | LOW |
| IXE 80 mg Q2W vs. PBO | 2.21 | 1.71 to 2.86 | MODERATE | 1.39 | 1.09 to 1.78 | LOW |
| IXE 80 mg Q4W vs. PBO | 2.25 | 1.59 to 3.18 | MODERATE | 1.41 | 1.10 to 1.79 | LOW |
| MTX 7.5 mg QW vs. PBO | 1.82 | 0.97 to 3.40 | LOW | n.d. | | |
| SEC 150 mg Q4W vs. PBO | 2.44 | 2.10 to 2.84 | HIGH | 1.03 | 0.95 to 1.12 | HIGH |
| SEC 150 mg Q4W + LD vs. PBO | 2.06 | 1.70 to 2.49 | HIGH | 1.01 | 0.89 to 1.15 | MODERATE |
| SEC 300 mg Q4W + LD vs. PBO | 2.28 | 1.87 to 2.80 | MODERATE | 1.02 | 0.89 to 1.16 | MODERATE |
| UST 45 mg W 0, 4 and Q12W vs. PBO | 1.95 | 1.52 to 2.50 | HIGH | n.d. | | |
| UST 90 mg W 0, 4 and Q12W* vs. PBO | 2.26 | 1.80 to 2.82 | MODERATE | 0.96 | 0.75 to1.24 | VERY LOW |

*One study (Gottlieb et al. 2009) reported induction dose of QW (weeks 0–3).
*Abbr.:* ACR20, 20 % improvement in American College of Rheumatology response criteria; RR, risk ratio; 95 % CI, 95 % confidence interval; ETA, etanercept; MTX, methotrexate; mg, milligrams; QW = once a week; INF, infliximab; kg, kilograms IXE, ixekizumab; ADA, adalimumab; Q2W, once every 2 weeks; EOW, every other week; PBO, placebo; APR, apremilast; BID, twice a day; CZP, certolizumab pegol; Q4W, once every 4 weeks; BIW, twice a week; W, week; Sec, secukinumab; LD, loading dose; UST, Ustekinumab; Q12W, every 12 weeks.

Local injection of glucocorticoids can be recommended in patients with active mono- or oligoarthritis, dactylitis with enthesitis or tendosynovitis.

Systemic usage of glucocorticoids should not be standard for treatment of psoriatic arthritis, but if needed, e.g., during flares, "systemic steroids at the lowest effective dose may be used with caution" [9]. Tapering of glucocorticoids should be done slowly and stepwise when feasible.

### Inflammatory bowel disease: How should psoriasis patients be managed with concomitant inflammatory bowel disease?

A narrative review of the existing literature and an assessment of the approval status of psoriasis therapies for Crohn's disease and ulcerative colitis were conducted. Existing guidelines were consulted [10–12].


 

Likely due to an overlap in the pathophysiology and genetic background of psoriasis and Crohn's disease, the risk of psoriasis patients developing Crohn's disease is approximately two- to threefold higher compared to the general population [13, 14].

The IL-17A antibody secukinumab and the IL-17RA antibody brodalumab have failed in studies in Crohn's disease, with some patients experiencing worsening of their disease during treatment [15, 16]. Cases of newly onset Crohn's disease and ulcerative colitis have been observed during treatment of psoriasis patients with IL-17 inhibitors. The observed signal is, however, low, and it is presently unclear if the rate exceeds the rate expected in a psoriasis population [17]. (For further information see additional background text in the long version.)

In contrast, ustekinumab, adalimumab, infliximab, and certolizumab are all targeted therapies approved not only for the treatment of psoriasis, but also for the treatment of Crohn's disease and, in the case of adalimumab, infliximab and ustekinumab, ulcerative colitis; dosages may vary between psoriasis and inflammatory bowel disease (IBD). Notably, the anti-TNF fusion protein etanercept failed in clinical trials in Crohn's disease [18].

There is an ongoing phase II/III clinical development program for the IL-23p19 inhibitors guselkumab and risankizumab in Crohn's disease and ulcerative colitis. In the case of risankizumab, positive clinical effects have been published for the induction and long term treatment of patients with Crohn's disease [19, 20] and are supported by immunological findings in the intestinal mucosa of patients with Crohn's disease receiving the drug [21]. There are several published case reports on the successful use of guselkumab in patients with Crohn's disease [22, 23].

Due to their intestinal side effect profile with a relatively frequent induction of abdominal pain, loose stools and diarrhea, fumarates should not be used in patients with inflammatory bowel disease (IBD). Severe gastrointestinal diseases are listed as contraindication in the prescription information of Fumaderm® and Skilarence®.

Inhibition of PDE4 with apremilast has shown positive effects in a phase II trial with ulcerative colitis [24].

Methotrexate has limited efficacy in Crohn's disease [25, 26] and probably even less in ulcerative colitis [27, 28], but there is a considerable body of experience and no signal for a worsening of these conditions.

Acitretin may be considered neutral in patients with psoriasis and inflammatory bowel disease and has been used in the treatment of patients with inflammatory bowel disease that developed psoriasiform lesions (including cases of so called paradoxical psoriasis) during treatment with TNF antagonist [29].

Ciclosporin (CsA) is frequently used in the treatment of steroid-refractory ulcerative colitis and has demonstrated long term outcomes similar to those of infliximab [30].

*Recommendations*

| | | |
|---|---|---|
| We *recommend* working in collaboration with the treating gastroenterologist when prescribing a systemic therapy in psoriasis patients with concomitant chronic inflammatory bowel disease. | ↑↑ | Strong consensus, consensus-based |
| In patients with psoriasis and active IBD or a history of IBD, we *recommend* preferentially using approved targeted therapies with a documented efficacy in these conditions:<br>*Crohn's disease:* anti-TNF (infliximab, adalimumab, certolizumab) and anti-IL-12/23p40 (ustekinumab).<br>*Ulcerative colitis:* anti-TNF (infliximab, adalimumab) and anti-IL-12/23p40 (ustekinumab). | ↑↑ | |
| If these first-choice treatments cannot be used, *we suggest* the following treatments to be considered as second choice targeted treatment options in patients with psoriasis and IBD:<br>*Crohn's disease:* anti-IL-23p19 (preferred risankizumab, guselkumab; also possible: tildrakizumab)<br>*Ulcerative colitis:* anti-IL-23p19 (preferred risankizumab, guselkumab; also possible: tildrakizumab) | ↑ | |
| If these first-choice treatments cannot be used, we *suggest* the following treatments to be considered as second choice oral treatment options in patients with psoriasis and IBD:<br>*Crohn's disease:* methotrexate.<br>*Active ulcerative colitis:* ciclosporin (preferred), apremilast (also possible). | ↑ | |

 

| | | |
|---|---|---|
| In combination with other treatments, we *suggest* acitretin as an adjunct therapy for patients with IBD and psoriasis, especially in cases with mild paradoxical psoriasis. | ↑ | Strong consensus, consensus-based |
| We suggest against the use of anti IL-17 antibodies in patients with inflammatory bowel disease. | ↓ | |

## Cancer: How should psoriasis patients with a history of malignancies be managed?

This chapter is based on the related chapter in previous versions of this guideline [1, 2]. A systematic search was conducted, details of which can be found in the Guideline Development Report. (For further information see additional background text in the long version of the guideline.)

*Association of therapy and incident cancer in psoriasis and other immune-mediated disease*

Some studies have studied the possible association of the use of systemic therapies for psoriasis and incident cancer (in patients without previous history of cancer).

A systematic review of RCTs and observational studies exploring the risk of cancer in psoriasis patients treated with biologics described an increased risk of non-melanoma skin cancer in those patients being treated with anti-TNFs. However, included studies lacked adjustment for highly relevant confounding factors such as prior phototherapy. Data on other cancers do not show a risk associated with exposure to drugs. However, the studies are likely to be underpowered to ascertain the risk of individual types of cancer [31]. Vaengebjerg et al. did not find increased risk of cancer in patients with psoriasis and psoriatic arthritis on biologics compared with other systemic therapies [32].

There are also some studies describing the risk of cancer associated with systemic therapy for other immune-mediated disorders, mainly rheumatoid arthritis, other rheumatic disorders and inflammatory bowel disease. Results in these disorders might not be appropriately extrapolated to psoriasis patients, as psoriatic patients receive less immunosuppressive therapy (specially corticosteroids) and the associated disorders are different [33].

Most studies are reassuring and did not find a relationship between exposure to anti-TNFs and risk of incident cancer in rheumatoid arthritis and psoriatic arthritis [34]. Luo et al., analyzing data from nine cohorts, described an increased risk of cancer in psoriatic arthritis patients treated with disease modifying antirheumatic drugs, which was not seen in patients receiving biologics. However, this increase was due to nonmelanoma skin cancer (NMSC) and included studies have not considered the likely effect of previous PUVA therapy [35]. Summary of Product Characteristics (SmPCs) of TNF inhibitors contain information regarding the risk of lymphoma/leukemia. However, these are rare events and data supporting this association are conflicting. So far, no such association have been shown for psoriasis patients [31].

*Risk of cancer recurrence in patients exposed to systemic therapy for psoriasis*

Few studies provide information that is relevant for answering this question.

Regarding patients with precancerous conditions (data available only for cervical dysplasia), a study using routine data of women with rheumatoid arthritis (RA), describe that initiation of therapy with a biological disease-modifying anti-rheumatic drug (bDMARD) was associated with an increased, but not statistically significant, risk of high-grade cervical dysplasia or cervical cancer compared to initiation of a nonbiological (nb)DMARD [36]. Conversely, a review analyzing 238 women with RA and a history of cervical carcinoma in situ, no genital cancer was observed in the TNF inhibitor (TNFi)-treated group over a median of 5.2 years of follow-up compared with two incidents of genital cancer in the nbDMARD-treated group, during a median follow-up of 3.9 years [37].

A systematic review of studies of patients with a history of cancer and exposed to anti-TNF therapy assessing for the risk of the occurrence of new cancer or cancer re-occurrence compared to nbDMARDs, included nine studies with 11,679 patients. None of them were studies on psoriasis. The outcome measures were heterogeneous, with many studies focused on describing NMSC. Overall, the study did not find an increased risk of recurrence in patients treated with anti-TNFs compared to nbDMARDs [38].

A retrospective study, based on routine data, of patients with rheumatoid arthritis and inflammatory bowel disease, and a previous NMSC, described an increased risk of a second NMSC in patients treated with methotrexate that was higher with longer exposures. Anti-TNF use was also associated with an increased risk, mostly in a subgroup (patients with RA and concomitant use of methotrexate) [39].

Another systematic review analyzed the risk of cancer recurrence in patients with immune-mediated diseases exposed to immune-suppressive therapies. They included 16 observational studies with 11,702 participants after a cancer diagnosis and with 1,698 new or recurrent cases of cancer. Only one very small study, and not contributing to the final analysis, was focused on psoriasis patients. Overall, rates of cancer recurrence were similar among participants receiving anti-TNF therapy, immune-modulator therapy or


 

no immunosuppression, but was higher among patients receiving combination immune suppression [40]. (For further information see additional background text in the long version of the guideline.)

| | | |
|---|---|---|
| We *recommend* taking the burden of psoriasis, and the risk of cancer worsening or recurrence (pre-cancer vs. low risk vs. high risk) into account for shared therapeutic decision making. | ↑↑ | Strong consensus, consensus-based |
| For patients with recent malignancy we *recommend* topical therapies, phototherapy (narrow band UVB)* and/or acitretin.<br>*Except patients with a recent and/or high risk of cutaneous malignancy. | ↑↑ | |
| We *recommend* discussing the decision to initiate immunosuppressive therapies in psoriasis patients with a current or recent diagnosis of cancer in the previous five years case-by-case with cancer specialists and to reach an informed decision, respecting the patient's preference. | ↑↑ | |
| In case of inadequate response to topical therapies, phototherapy (narrow band UVB), and/or acitretin we *suggest* using MTX in psoriasis patients with a previous history of cancer.<br>**For patients with history of nonmelanoma skin cancer, see background text. | ↑ | |
| We *suggest* apremilast can be used in psoriasis patients with a previous history of cancer despite the lack of long-term experience based on pathophysiological considerations on a case-by-case basis including discussion with cancer specialist | ↑ | |
| We *suggested against* using ciclosporin in psoriasis patients with a previous history of cancer. | ↓ | |
| We *suggest* anti-TNF or ustekinumab can be used based on existing safety data on a case-by-case basis including discussion with cancer specialist.<br>We *suggest* anti-IL17 or anti IL23 can be used in psoriasis patients with a previous history of cancer despite the lack of long-term experience based on pathophysiological considerations on a case-by-case basis including discussion with a cancer specialist. | ↑ | |

## Depression: How should psoriasis patients with a history of depression and/or suicidal ideation be managed?

This chapter is based on the related chapter in previous versions of this guideline [1, 2]. A systematic search was conducted, details of which can be found in the Guideline Development Report.

*Recommendations*

Psoriasis is associated with a higher risk for psychiatric comorbidities including anxiety and depression while results on suicide ideation and suicide are more unclear [12, 41–44]. In general, interventions that are effective for psoriasis correspondingly also improve symptoms of depression. Clinical studies using adalimumab, etanercept, ustekinumab, ixekizumab, guselkumab or fumarates for the treatment of psoriasis have shown that all these anti-inflammatory drugs not only improve psoriatic manifestations, but also symptoms of depression [43, 45–50]. (For further information see additional background text in the long version of the guideline.)

*Acitretin*

Acitretin has been reported to be associated with depression in some case reports [51, 52]. However, more recent reviews of the literature conclude that except for very few cases of depression and suicidal ideation there are no convincing evidence-based data to support an association between acitretin and depression/suicidality [53, 54]. A formal review of retinoids (including acitretin and isotretinoin) carried out by

 

the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in 2018 [55] concluded that it was not possible to identify a clear increase in the risk of neuropsychiatric disorders in people taking oral retinoids compared to those that did not. However, the EMA decided to include a warning about the possible risk in the product information for oral retinoids, since PRAC noticed that severe skin disorders themselves increase the risk of psychiatric disorders [56]. Based on the above, the guideline group did not consider there to be sufficient evidence to specifically counsel against use of acitretin in those patients with mood disorders but, in common with all systemic therapies, clinicians should monitor for mood changes given that people with psoriasis are at increased risk of anxiety and depression.

*Brodalumab*

In two out of three phase III studies of efficacy and safety of brodalumab in patients with plaque psoriasis (AMAGINE 1–3) cases of suicide were reported (two patients in each of studies 1 and 2) [57, 58]. An expert opinion (2019) discussing these observed cases of suicide highlighted the following aspects [59]: Further review of the suicides by the Columbia Classification Algorithm of Suicide Assessment Review Board confirmed only three of the cases as suicides. All of them had underlying psychiatric disorders or stressors and all three suicides occurred at one center. Both symptoms of depression and anxiety decreased during treatment with brodalumab [58].

In the European SmPC, the reported suicidal ideation and behavior, including completed suicide in patients treated with brodalumab was mentioned. However, it was also stated that a causal association between treatment with brodalumab and increased risk of suicidal ideation and behavior has not been established. In the SmPC, it is recommended that risk and benefit of treatment with brodalumab should be carefully weighed for patients with a history of depression and/or suicidal ideation. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behavior is identified, it was recommended to discontinue treatment with brodalumab [60].

*Apremilast*

Results from two phase III studies including patients with moderate-to-severe psoriasis (ESTEEM 1 and ESTEEM 2) with open-label extension for up to four years, showed that patient reported depression occurred in 1.4 % of patients treated with apremilast and in 0.5 % of receiving placebo. The incidence of depression did not increase over time. There was one suicide attempt, and no completed suicides with apremilast [61]. Similar results were achieved in an open-label extension study (for up to additional four years) of three phase III studies of patients with psoriatic arthritis (PsA); 1.2 % in patients treated with apremilast and 0.8 % in patients receiving placebo. There were two suicide attempts, and no completed suicides with apremilast [62]. Post-marketing experience, including five cases of completed suicides, was reported and a new safety information was published for apremilast provided by Celgene in agreement with the EMA and the UK Medicine and Healthcare Products Regulatory Authority in 2016 [63]. In here it was stated that evidence from clinical trials and post-marketing experience suggested a causal association between suicidal ideation and behavior with the use of apremilast. The SmPC and patient leaflet for apremilast was updated to add a warning about depression (common adverse reaction [≥ 1/100 to < 1/10]) and suicidal behavior and ideation (uncommon adverse reaction [≥ 1/1,000 to < 1/100]) [64]. (For further information see additional background text in the long version of the guideline.)

| | | |
|---|---|---|
| We *recommend* being aware of signs and symptoms of anxiety and depression in patients with psoriasis and monitoring for symptoms of depression and/or suicidal ideation or anxiety during systemic treatments for psoriasis, especially in those with a history of any of the above. | ↑↑ | Strong consensus, consensus-based |
| We *suggest* using alternatives to brodalumab and apremilast in patients with a history of depression and/or suicidal ideation. | ↑ | |

## Diabetes: How should psoriasis patients with diabetes mellitus be managed?

A systematic review was conducted. Four prospective studies (Oxford level 2) and four retrospective studies (Oxford level 3) were included. For details, please refer to the Guideline Development Report and Appendix 5 of the Evidence Report.

*Recommendations*

(For further information see additional background text in the long version of the guideline.) Short-term treatment with methotrexate does not appear to have a negative effect on carbohydrate metabolism parameters in patients with psoriasis


 

or psoriatic arthritis [65–67]. However, MTX should be administered with caution in the case of diabetes and obesity, due to the increased risk of hepatic fibrosis especially when the cumulative dose exceeds 1.5 g [68, 69]. Ciclosporin can increase insulin resistance, interfere with fatty acid metabolism favoring the development of dyslipidemia and the increase of serum uric acid [70]. The diabetogenic effect of CsA has been assumed to be related to inhibition of insulin secretion from pancreas islet cells [71], an effect that may be even more relevant in obese psoriatic patients. Acitretin effects on insulin resistance are not clearly established. There is no evidence that fumarates and apremilast could affect insulin resistance. Additionally, diabetes is not a contraindication for the use of apremilast or fumarates. For patients with renal impairment due to diabetic nephropathy, limitations apply of fumarates as stated in the SmPC.

Clinically significant dyslipidemia has been rarely reported in patients receiving TNFα antagonists, but this is not a common issue in clinical practice [72]. Body weight gain could occur in patients treated with TNFα antagonists [73, 74]. In contrast, ustekinumab and IL-17 inhibitors usually do not increase body weight in patients with chronic plaque psoriasis [75, 76]. Apremilast has been shown to cause weight loss in clinical trials [76]. (For further information see additional background text in the long version of the guideline.)

Finally, patients with moderate-to-severe psoriasis are candidate for interventions aimed to reduce their cardiovascular risk profile. Screening for cardiovascular risks including diabetes, hypertension and dyslipidemia should be recommended for all psoriasis patients [12]. Non-pharmacological interventions, such as weight loss, should be recommended to obese patients. Indeed, it has been reported that a low-calorie diet inducing a moderate weight loss (i.e. 5 to 10 % of body weight) increases the responsiveness of obese patients with moderate-to-severe chronic plaque psoriasis to systemic treatments [77–80]. Moreover, body weight loss could also increase insulin sensitivity in obese patients with psoriasis. (For further information see additional background text in the long version of the guideline.)

Finally, it should be considered that diabetic nephropathy occurring in patients with psoriasis could reduce the clearance of any systemic treatments for psoriasis including MTX and CsA [81, 82]. Ciclosporin should be considered cautiously in patients with diabetes mellitus as significantly increased serum creatinine concentration could be observed [83].

| | | |
|---|---|---|
| We *suggest against* using ciclosporin or MTX as a first line treatment in patients with diabetes and/or features of the metabolic syndrome. | ↓ | Consensus, consensus-based |
| We *suggest against* using acitretin or ciclosporin as a first line treatment in patients with dyslipidemia. | ↓ | Strong consensus, consensus-based |

## Heart disease: How should psoriasis patients with ischemic heart disease and/or congestive heart failure be managed?

This chapter is based on the related chapter in previous versions of this guideline [1, 2]. A systematic search was conducted, details of which can be found in the Guideline Development Report.

### Recommendations

#### Ischemic heart disease/atherosclerosis

*Summary/key points (for further information see additional background text in the long version of the guideline)*

- Patients with psoriasis have an approximately two to threefold increased relative risk for developing cardiovascular events such as myocardial infarction or stroke compared to individuals without psoriasis. The cardiovascular risk seems to correlate with disease severity. The link between psoriasis and cardiovascular disease is likely to be driven by an increased prevalence of classical cardiovascular risk factors among patients with psoriasis such as the components of the metabolic syndrome. There is also evidence for an independent risk conferred by the systemic inflammatory nature of the disease.
- A careful history should be obtained from all patients to determine whether they have established cardiovascular disease. Appropriate investigations and treatment should be initiated in accordance with current European Society of Cardiology (ESC) guidance [84].
- Patients without a history of cardiovascular disease, should have their cardiovascular risk factors assessed and be given lifestyle advice including avoiding smoking, maintaining a healthy diet, increasing physical activity and maintaining a healthy blood pressure with other treatments in accordance with current ESC guidance [85, 86].
- With the exception of methotrexate, there are no studies formally evaluating the effect of any anti-psoriatic therapy as a treatment for coronary heart disease. In general, it seems that the reduction of psoriatic inflammation is beneficial in psoriatic patients with cardiovascular comorbidity (indirect effect), but direct effects of treatments for psoriasis on atherosclerotic inflammation may also play a role [87].
- Multiple studies with different therapies have produced evidence on parameters of cardiovascular risk and/or

 

assessed cardiovascular events during the treatment of patients with psoriasis.

- From these studies it appears that MTX, the anti-TNFs (studies available especially on adalimumab), and ustekinumab and the IL-17-antagonists (studies available especially on secukinumab) improve parameters of cardiovascular risk in patients with psoriasis.
- While in some experimental models IL-17 has been associated with stabilizing properties of unstable atherosclerotic disease, treatment with IL-17 inhibitors has not been associated with an increased rate of cardiovascular events [88]. Moreover, inhibition of IL-17 (studies available especially on secukinumab), has shown to improve surrogate markers of endothelial dysfunction [89, 90].
- The data available on inhibitors of IL-23p19 indicate that they are safe in patients with cardiovascular comorbidity, but information on their potential effects on cardiovascular factors risk is limited.
- Treatment with apremilast is associated with weight loss in some patients. Experimental studies indicate potentially beneficial effects of apremilast in models of atherosclerosis. Neither clinical trial data nor observational studies indicate that apremilast is associated with an increased risk of cardiovascular events in psoriasis patients with ischemic heart disease or cardiovascular risk factors.
- There is no evidence that fumarates are associated with increased cardiovascular events in patients with ischemic heart disease.
- Ciclosporin may induce or worsen arterial hypertension, a condition often found in patients with ischemic heart disease, and worsen dyslipidemia. The metabolism of ciclosporin may interfere with drugs used in patients with ischemic heart disease such as beta-blockers or calcium antagonists.
- Acitretin has very limited anti-inflammatory potential and may induce or worsen hyperlipidemia.

| | | |
|---|---|---|
| We *suggest against* ciclosporin or acitretin as preferred treatments in patients with psoriasis and ischemic heart disease. | ↓ | Strong consensus, consensus-based |
| We *suggest* methotrexate as preferred first-line therapy in patients with psoriasis and ischemic heart disease* if other patient characteristics do not preclude its use. In case of concomitant congestive heart failure, also note the recommendations from the respective section. | ↑ | |
| We *suggest* anti-TNFs, ustekinumab, and IL-17 inhibitors as preferred targeted therapies in patients with psoriasis and ischemic heart disease*. In case of concomitant congestive heart failure, also note the recommendations from the respective section. | ↑ | |

## Heart failure

*Summary (for further information see additional background text in the long version of the guideline)*

- Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [85].
- Common causes include coronary artery disease (previous myocardial infarction), arterial hypertension, atrial fibrillation, valvular heart disease and cardiomyopathies. The condition may, therefore, co-exist with ischemic heart disease.
- Patients with suspected or confirmed heart failure should be referred to a cardiologist for investigation and treatment in accordance with current ESC guidance [91].
- The *New York Heart Association* (NYHA) functional classification is commonly used to describe the severity of symptoms and exercise intolerance in patients with heart failure (https://manual.jointcommission.org/releases/TJC2018A/DataElem0439.html):
  - *Class I:* No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.
  - *Class II:* Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
  - *Class III:* Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
  - *Class IV:* Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
- There is evidence that anti-TNFs, especially adalimumab, certolizumab pegol and infliximab, worsen advanced heart failure and both drugs are contraindicated in patients with congestive heart failure NYHA III/IV and must be used with caution in patients with milder forms


 

of congestive heart failure (NYHA I/II). Etanercept must be used with caution in patients with congestive heart failure.

- The use of other targeted therapies in patients with psoriasis and congestive heart failure seems to be neutral depending on the underlying cause (caution infection).
- The use of methotrexate, acitretin and apremilast in patients with psoriasis and heart failure seems to be neutral depending on the underlying cause.
- Ciclosporin may increase the blood pressure and reduce kidney function in patients with psoriasis and heart failure and interfere with many drugs used in the treatment of this condition.
- Fumarates may reduce kidney function in patients with psoriasis and heart failure.

| | | |
|---|---|---|
| We *suggest against* using ciclosporin in patients with psoriasis and advanced congestive heart failure. | ↓ | Strong consensus, consensus-based |
| We *suggest* that methotrexate, acitretin and apremilast be considered as treatment in patients with psoriasis and advanced congestive heart failure*. *In case of concomitant ischemic heart failure, also note the recommendations from the respective section. | ↑ | |
| We *suggest* that ustekinumab, inhibitors of IL-17 and of IL-23 be considered as treatment in patients with psoriasis and advanced congestive heart failure*. *In case of concomitant ischemic heart failure, also note the recommendations from the respective section. | ↑ | |
| We *recommend against* using anti-TNFs in patients with psoriasis and advanced congestive heart failure | ↓↓ | |
| We *recommend* discussing the choice of a systemic therapy in psoriasis patients with advanced congestive heart failure with a cardiologist. | ↑↑ | |

**Kidney disease: How should psoriasis patients with kidney failure/renal impairment be managed?**

A narrative review of the existing literature was conducted.

## Recommendations

A number of risk factors that predispose one to chronic kidney disease (CKD) are especially prevalent in people with multiple comorbidities including diabetes, hypertension, cardiovascular disease, being treated with drugs that may impair kidney function. A UK population-based study suggests that the risk of CKD was increased in people with moderate-to-severe psoriasis, independent of these risk factors [92]. Thus, the optimal choice of systemic therapy in the context of CKD is likely to be a relatively common clinical scenario. This is supported by data from the Spanish long-term pharmacovigilance registry indicating that 13 % of the total cohort were categorized as having "chronic renal failure" [93].

In people with established CKD, the following factors were considered when evaluating the treatment options for psoriasis:

- the likely effect of the psoriasis treatment on residual kidney function,
- the impact of CKD on pharmacokinetics/pharmacodynamics of the psoriasis treatment,
- potential drug interactions,
- associated CKD co-morbidity.

## Systemic therapies

*Acitretin*

In summary, acitretin is not known to be nephrotoxic, and CKD (any stage) would not be predicted to markedly impact on drug disposition. (For further information see additional background text in the long version of the guideline.)

*Apremilast*

Apremilast has no known nephrotoxic potential. In the pivotal clinical trials there was no evidence for treatment emergent adverse events (AEs) related to renal function [64, 94].

In patients with mild to moderate impairment of kidney function, no dose adjustment of apremilast is necessary. When patients have severe impairment of kidney function (eGFR below 30 mL/min/1,73 $m^2$ or CLcr < 30 mL/min) the dose of apremilast should be reduced to 30 mg once daily. (For further information see additional background text in the long version of the guideline.)

 

### Fumarates

Fumarates are known to be potentially nephrotoxic, and may rarely cause an irreversible, proximal renal tubular nephropathy with long-term use. Recent studies [95] of dimethyl fumarate (for MS) confirm proteinuria and reduction in eGFR to occur more commonly than placebo; German guidelines and the SmPC specify careful monitoring of serum creatinine, and treatment cessation in the event of significant change. In healthy individuals, fumarates are extensively metabolized by ubiquitous esterases, and so CKD would not be predicted to significantly impact on drug clearance [96, 97].

### Ciclosporin

Ciclosporin has established nephrotoxic potential. Acute nephrotoxicity can occur within weeks of treatment initiation, is reversible, and arises due to dose-dependent vascular dysfunction, involving afferent arteriolar constriction that leads to increased vascular resistance and a decrease in glomerular filtration rate. Tubular dysfunction may also occur, characterized by decreased magnesium re-absorption, decreased uric acid excretion, decreased potassium and hydrogen ion secretion, and distal tubular acidosis. Chronic nephrotoxicity [98, 99] is largely irreversible and is characterized by progressive arteriolar hyalinosis, interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Chronic nephrotoxicity is more likely to occur with higher daily doses, larger cumulative doses and long-term therapy (more than 1–2 years). (For further information see additional background text in the long version of the guideline.)

### Methotrexate

Methotrexate is not generally considered nephrotoxic when used at low doses for inflammatory disease, although renal impairment is reported [100], and may be an under-recognized event. Methotrexate and 7-hydroxymethotrexate are mainly excreted through the kidneys, via glomerular filtration and active transport. Methotrexate clearance is therefore reduced (and thus risk of toxicity increased) in the context of CKD, depending on the stage. (For further information see additional background text in the long version of the guideline.)

### Biological therapy

To date, nephrotoxicity has not been reported as an AE in relation to any groups of biologic agents (TNF antagonists, IL-17A/IL-17RA antagonists, IL-12/23p40 antagonists, and IL-23p19 antagonists). Clearance of biological therapies should not be affected in case of CKD (of any stage).

| | | |
|---|---|---|
| We *recommend* ensuring an accurate assessment of renal function in any psoriasis patient with known or suspected chronic kidney disease prior to therapy. | ↑↑ | Strong consensus, consensus-based |
| We *recommend* working in collaboration with the nephrologist when prescribing a systemic therapy that is secreted via the kidneys or that may affect kidney function in any psoriasis patient with chronic kidney disease of stage 3 (eGFR < 60 mL/min/1.73 m²) or more. | ↑↑ | |
| We *suggest* acitretin*, apremilast*, fumarates*, methotrexate* *may be used* in psoriasis patients with *mild to moderate renal impairment* (eGFR ≥ 30 mL/min/1.73 m²) *Careful dosing/dose adjustment may be needed; for apremilast if < 30 mL/min/1.73 m². | ↑ | |
| We *suggest* using biologics in psoriasis patients with chronic kidney disease and all stages of renal impairment. | ↑ | |
| We *recommend against* using ciclosporin, fumarates, or methotrexate in psoriasis patients with *chronic kidney disease and severe renal* impairment (eGFR < 30 mL/min/1.73 m²). | ↓↓ | |

## Neurological diseases: Which treatments are appropriate for psoriasis patients with neurological diseases?

A narrative review of the existing literature was conducted. (For further information see additional background text in the long version of the guideline.)

### Summary of recommendations

With the exception of TNF antagonists, any of the standard or biologic treatments can be used in people with


 

co-existing neurological disease. Although neurotoxicity is reported with CsA, and (rarely) with MTX, there is no evidence that those with pre-existing neurological disease are more at risk. The causal association between TNF antagonists and demyelination remains yet to be proven, although accumulating anecdotal reports, biological plausibility and expert consensus indicate that this class of drugs should be avoided in patients with a clear history of central demyelination. Given evidence for a genetic basis to multiple sclerosis (MS) [101], and that asymptomatic first-degree relatives may have morphological evidence of subclinical disease and/or cerebrospinal fluid (CSF) oligoclonal bands (reviewed in [102]), it would seem prudent to use TNF antagonists with caution in this group too. Dimethyl fumarate is licensed for use in MS, and so may be a preferred first line option, however, surveillance monitoring of peripheral leukocyte counts is strongly recommended in order to minimize the risk of progressive multifocal leukoencephalopathy (PML). Ustekinumab and anti-IL-17 represent alternative treatment options.

| | | |
|---|---|---|
| We *suggest* using fumarates in psoriasis patients with multiple sclerosis. | ↑ | Strong consensus, consensus-based |
| We *recommend against* using TNF antagonist therapy in psoriasis patients with a diagnosis of multiple sclerosis or other demyelinating disease. | ↓↓ | |
| In psoriasis patients with a first-degree relative with multiple sclerosis or other demyelinating disease, we *suggest against* the use of TNF antagonist therapy if other suitable treatment options are available. | ↓ | |

### Viral hepatitis: When and how should psoriasis patients be screened for viral hepatitis and how should patients who test positive be managed?

A systematic review on the treatment of psoriasis patients with viral hepatitis was conducted, which included 22 studies (Oxford level 3). For details, please refer to the Guideline Development Report and Appendix 7 of the Evidence Report.

## Recommendations

### Screening

| | | |
|---|---|---|
| We *recommend against* screening for *hepatitis A* as a routine measure before starting a systemic treatment. | ↓↓ | Strong consensus, consensus-based |
| We *recommend* screening patients for *hepatitis B* (HBsAg, anti-HBsAg, anti-HBcAg) as a routine measure before starting a treatment with ciclosporin, methotrexate or biologics. | ↑↑ | Strong consensus, consensus-based |
| We *recommend* following the algorithm presented in Figure 1 for the interpretation of the *hepatitis B* test results. | ↑↑ | |
| We *recommend* screening patients for *hepatitis C* as a routine measure before starting a treatment with methotrexate or biologics. | ↑↑ | Strong consensus, consensus-based |
| In case of positive findings for *hepatitis C*, we *recommend* referral to a hepatologist. | ↑↑ | |

*Choice of treatment*

| | | |
|---|---|---|
| We *recommend* that the treatment decision for patients with positive test result for HBsAg or positive HBV DNA should always be taken together with a hepatologist. | ↑↑ | Strong consensus, consensus-based |
| Depending on the individual health care setting and personal experience and training, we *suggest* consulting with a hepatologist to choose a systemic treatment for patients that have a positive anti-HBc with a neg. HBsAg/HBV-DNA test. We *suggest*, based on the common practice within the guideline group, acitretin, apremilast, fumarates, MTX, ustekinumab and the anti-IL-17 and anti-IL-23 antibodies as preferred systemic treatment options for this patient group. | ↑↑ | Strong consensus evidence- and consensus-based (see Guideline Development Report and Evidence Report) |

 

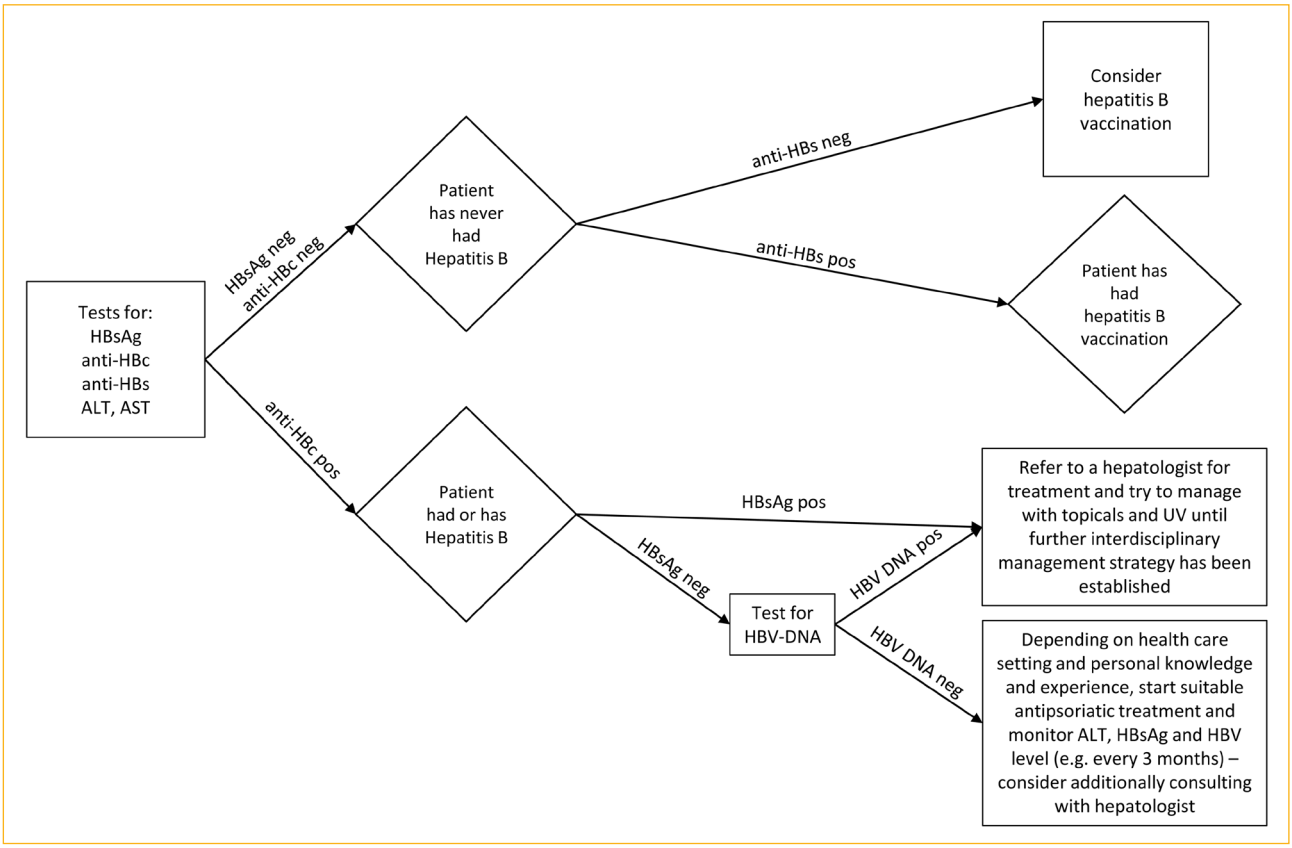


**Figure 1** Algorithm for the interpretation of the hepatitis B test results.

| | | |
|---|---|---|
| We *recommend* regular testing for HBsAG/HBV-DNA (e.g., every three months) during systemic treatment. | ↑↑ | Strong consensus, consensus-based |
| We *recommend* recording all treatment initiations and follow up visits of psoriasis patients with concomitant hepatitis B or C cases in drug registries | ↑↑ | Strong consensus, consensus-based |

The available data published is insufficient to give strong recommendations for or against using the available antipsoriatic drugs in patients with moderate-to-severe psoriasis and concomitant hepatitis B. An overview table in the long version of the guideline offers a summary of reported cases of reactivation. Reported cases need to be seen in correlation to approval date, especially with years and numbers of psoriasis patients with hepatitis exposed to the drug. For detailed information, see the Guideline Development Report.

For some of the treatments, hepatitis is mentioned as a contraindication in the SmPC, although clinical practice, available case series or registry data may indicate a safety profile in line with treatments where this is not mentioned as a contraindication. This hold particularly true for methotrexate, where study data indicates at least no increase in liver fibrosis [103].

## Tuberculosis: How to screen for tuberculosis before and during biologic treatment?

This chapter is based on the related chapter in previous versions of the guideline [1, 2]. A systematic search was conducted, details of which can be found in the Guideline Development Report.

This chapter will focus on screening and the next chapter on management in case of unclear tuberculosis (TB) status and/or suspicion of latent tuberculosis.

### Recommendations

| | | |
|---|---|---|
| We *recommend* excluding the diagnosis of tuberculosis using an IGRA (interferon gamma release assay) and a chest X-ray before initiating treatment with MTX or a biologic agent. | ↑↑ | Strong consensus, consensus-based |


 

| | | |
|---|---|---|
| We *recommend* a repeat IGRA and chest X-ray if tuberculosis reactivation is suspected or if there is a risk of a new infection under biologic therapy. For this purpose, we *recommend* an individual risk assessment for each patient. | ↑↑ | Strong consensus, consensus-based |

### IGRA

The interferon gamma release assay is a specific blood test. It is not affected by prior BCG vaccination, but interpreting borderline results can be limited due to issues in the cut-off values, shifting conversion and reversion rates over time, and varying test reproducibility. The interferon gamma release assay does not allow for differentiation between active or latent TB [104]. A suppressed immune system (e.g., due to antipsoriatic medication) reduces the sensitivity of tests based on T cell responses. Only positive results will be convincing in that case, while negative results cannot rule out a TB infection. Negative results of a tuberculin skin test (TST) or IGRA of HIV-infected patients with a low CD4 count cannot rule out a TB infection.

### Screening during biologic treatment

Whether to re-screen during, or after a longer interruption and resumption of, biologic therapy depends in large part on the patient's medical history and clinical examination. The approach is not fundamentally different from that used for initial tuberculosis screening. Because there are no definite recommendations regarding the duration of a therapy interruption, a patient's medical history is also decisive in this regard. In some centers, screening is usually repeated if therapy or care is interrupted for more than twelve months.

## Tuberculosis: How to manage psoriasis in patients with positive tuberculosis test results?

This chapter is based on the related chapter in previous versions of the guideline [1, 2]. A systematic search was conducted, the details of which can be found in the Guideline Development Report.

# Interpretation of positive findings in IGRA

The interferon gamma release assay is a specific blood test. The interpretation of IGRA test results (especially borderline results) can be limited due to issues in the cut-off values, shifting conversions and reversion rates over time, and varying test reproducibility. In case of borderline results, repeating the test may be advisable [104].

Means to distinguish between active and latent TB commonly used in the guidelines group experts' setting include medical history (exposure risk), signs and symptoms (e.g., current cough, fever, weight loss, night sweats), chest x-ray [105] and urinalysis (pyuria) [106–108]. For details of differential diagnosis of latent versus active TB, please see respective guidelines and reviews [104, 105, 109].

# Risk of TBC reactivation with different treatments

## Conventional treatments/Small molecules

Data on reactivation risk with acitretin, ciclosporin, fumaric acid esters and methotrexate and apremilast is scarce. Most published guidelines so far have not recommended TB screening for these drugs (except MTX and CsA) [110]. Screening before treatment for MTX is recommended in the SmPC. The sensitivity of IGRA and the tuberculin skin test (TST) may be influenced by conventional immunosuppressive treatments, so doing IGRA initially may be beneficial if a later switch, specially from MTX to other drug categories appears likely [111].

### Biologics

A higher risk of latent TB reactivation has been identified with (in descending order of risk): infliximab, adalimumab and etanercept. Cases of latent TB reactivation with ustekinumab have been reported in a long-term study of up to five years [112]. The risk of latent TB reactivation seems to be lowest during treatment with anti-IL-17 and anti-IL-23 targeted treatments [34, 113].

In a systematic review by Snast et al., 78 patients who developed active TB during biologic treatment were analyzed. Eighty percent of all cases were treated with adalimumab or infliximab, 12 % were treated with etanercept. No case of active TB was identified with the anti-interleukin-17 agents (ixekizumab, secukinumab, and brodalumab). However, the total patient exposure years for these at the time of analysis were much shorter than for the TNF antagonists. All patients in this review had initially been screened for TB. In the majority of cases, patients had no risk factors for primary TB or active TB and presented mostly with extra-pulmonary disease within the first six months of biologic therapy [114].

The long version of the guideline contains a table with an overview of the screening recommendations according to the SmPC and a presentation of the data on reports of reactivation under antipsoriatic treatments. The risk assessment may be biased due to the different time periods when the cases occurred. At the time of TNF alpha introduction, TBC screening was not always done, leading to higher numbers

 

of patients with TB being exposed to the respective drugs. In addition to the reported cases of TB reactivation, pathophysiological considerations of the immune response to TB favor the group of anti-IL-17 and anti-IL-23 as treatment options. Interleukin 12 has been reported to play a role in the anti TB immune response.

| | | |
|---|---|---|
| We *recommend* discussing the decision to initiate immuno-suppressive therapies and the need for a prophylactic anti TB treatment in patients with signs for latent tuberculosis case by case with an infectious disease specialist. | ↑↑ | Strong consensus, consensus-based |
| As a commonly used procedure in case of latent TB, we *suggest* a prophylactic treatment with isoniazid 300 mg for nine months or rifampicin 600 mg for four months with treatment initiation one month before the start of the immunosuppressive therapy. | ↑ | |
| We *recommend against* TNF alpha antagonists as a treatment for patients with latent TB unless there are no other suitable treatment options. | ↓↓ | |
| We *recommend* remaining alert to signs and symptoms of tuberculosis reactivation during therapy. | ↑↑ | |
| For patients with latent TB who require systemic therapy, we *suggest* choosing one of the following options: acitretin or apremilast or fumaric acid esters/dimethyl fumarate or a treatment from the anti-17 or anti-23 group. | ↑ | |

### Wish for child/pregnancy: How should psoriasis patients with a wish for pregnancy in the near future or who are pregnant be managed?

This chapter is based on the related chapter in previous versions of this guideline [1, 2]. A systematic search was conducted, details of which can be found in the Guideline Development Report.

## Recommendations

Psoriasis commonly affects men and women planning conception and women who are pregnant, so understanding the risks of therapy during conception and pregnancy is crucial. Psoriasis is not known to have a significant impact on either male or female fertility. Although pregnancy has an unpredictable effect on psoriasis, limited evidence suggests that psoriasis usually improves; around 55 % improve during pregnancy, 25 % report no change, and 25 % worsen [115, 116]. Conversely in the post-partum period, psoriasis is more likely to flare; around 65 % worsen, 25 % demonstrate no change and 10 % improve.

Maternal and fetal health outcomes are vital considerations when deciding on the optimal treatment for individuals with psoriasis who are planning conception or are pregnant. Although data are limited and not always consistent across studies [117], untreated severe psoriasis in the mother may be detrimental for fetal well-being and pregnancy outcomes, for example it has been shown to be associated with preterm birth and low birthweight babies [118, 119]. The risk of untreated psoriasis of the mother in pregnancy must therefore be weighed against any potential harm through drug exposure of the fetus. (For further information see additional background text in the long version of the guideline.)

## Non-biologic systemic drugs

For further information on acitretin, apremilast, ciclosporin, fumarates and methotrexate see additional background text in the long version of the guideline.

## Recommendations (non-biologic systemic drugs)

When providing advice on use of systemic therapies in women planning conception or who are pregnant, prescribers are advised to use these recommendations with reference to the individual drug SmPC.

| | | |
|---|---|---|
| Methotrexate and acitretin are contra-indicated in women planning conception. We *recommend against* using these. | ↓↓ | Strong consensus, consensus-based |
| Fumarates and apremilast are contra-indicated in women planning conception. We *suggest against* using these. | ↓ | |


 

| | | |
|---|---|---|
| We *recommend* consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems. | ↑↑ | Strong consensus, consensus-based |
| We *recommend* the collection of maternal exposure to medications and pregnancy outcome data in a respective safety registry. | ↑↑ | |

## Biologic drugs

(For further information see additional background text in the long version of the guideline.)

All of the biologic agents that are currently licensed for psoriasis except certolizumab pegol contain a human IgG1 Fc region and are actively transported across the placenta via neonatal Fc receptors [120, 121]. Active placental transfer is thought to be very low during the first trimester when organogenesis takes place, hence the theoretical risk of teratogenicity of biologics is low. Active transfer can, however, occur at around 13 weeks' gestation and increases significantly after 20 weeks' gestation. This increasing exposure to biologics during the second and third trimesters is hypothesized to adversely affect fetal development, leading to potential risk of neonatal immunosuppression and greater risk of neonatal infections [122]. Biologic therapies typically disappear from an infant's serum within the first six months of life.

In contrast, certolizumab pegol is the only PEGylated humanized antigen-binding fragment of a TNF antagonist and it lacks a Fc domain [123]. Certolizumab pegol therefore does not bind to the human neonatal Fc receptor and it is not actively transferred across the placenta. This was underscored by an analysis of 31 pregnancies exposed to infliximab, adalimumab and certolizumab pegol (for inflammatory bowel disease), in which the median levels of infliximab, adalimumab and certolizumab pegol in the cord blood of infants compared with that of mother were 160 %, 153 %, and 3.9 %, respectively [124]. Infliximab and adalimumab could be detected in the infants for as long as six months. Post-marketing prospective pharmacokinetic research has confirmed no/minimal transfer of certolizumab pegol via the placenta (CRIB study, n = 16 [125]) and into breast milk (CRADLE study, n = 19 [126]).

Population-based cohort studies that report pregnancy outcomes in women exposed to biologics during conception and/or pregnancy are limited to TNF antagonist exposure only [127–139] (see respective table in the Methods & Evidence Report of the EuroGuidDerm version of the guideline).

No evidence was identified on the use of IL-12/IL-23p40, IL-17 or IL-23p19 inhibitor biologics. Overall, the available studies identified no clear evidence of drug-specific harm to the fetus following TNF antagonist exposure with respect to congenital malformations, live births, pre-term births or neonatal infections [127–139]. (For further information see additional background text in the long version of the guideline.)

## Recommendations (biologic drugs)

When providing advice on use of systemic therapies in women planning conception or who are pregnant, prescribers are advised to use these recommendations with reference to the individual drug SmPC.

All biologic drugs currently licensed for psoriasis (with the exception of certolizumab pegol) are actively transferred to the fetus during the second and third trimester, and the impact of this on neonatal development and risk of infection (to both mother and baby) has not been adequately studied.

| | | |
|---|---|---|
| We *suggest* stopping biologic therapy in the second and third trimester (except certolizumab pegol) to minimize fetal exposure and limit potential infection risk to the neonate. | ↑ | Strong consensus, consensus-based |
| We *suggest* certolizumab pegol as a first line choice when starting biologic therapy in women planning conception (when a biologic is considered essential to use in pregnancy) and when it is necessary to start a systemic therapy during the second or third trimester. | ↑ | |
| We *suggest against* using live or live attenuated vaccines in infants (up to 6 months of age) whose mothers received biologic therapy beyond 16 weeks gestation, unless the benefit of the vaccination clearly outweighs the theoretical risk of administration. | ↓ | |
| We *recommend* consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems | ↑↑ | |

 

| | | |
|---|---|---|
| We *recommend* the collection of maternal exposure to medications and pregnancy outcome data in a respective safety registry. | ↑↑ | Strong consensus, consensus-based |

## Necessity of continuing contraception immediately following biologic treatment cessation

(For further information see additional background text in the long version of the guideline.)

## Paternal use

For paternal use of acitretin, apremilast, ciclosporin, fumarates, methotrexate and biologics see additional background text in the long version of the guideline.

| | | |
|---|---|---|
| We *recommend* that men discontinue methotrexate three months before attempting conception*.<br>*EMA recommends six months as a means of precaution; the practice of the guideline group differs from this. | ↑↑ | Strong consensus, consensus-based |
| As a precaution, we *suggest* that men taking acitretin use barrier forms of contraception post-conception to limit exposure via direct contact with semen during pregnancy. | ↑ | |
| We *recommend* the collection of paternal exposure to medications during conception and pregnancy outcome data in national safety registries where available. | ↑↑ | |

For chapters 3.13. (Vaccinations) and 3.14. (Immunogenicity) see long version of the guideline.

For chapter 3.15. (Covid-19), a narrative review of the existing literature was conducted in late April 2020. The most up to date version of this chapter can be found alongside the main guideline document on the EDF website.

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### Conflict of interest

*For authors of the German guideline:* See Guideline Development Report.

*For authors of the EuroGuiDerm guideline:* See EuroGuiDerm Guideline on the systemic treatment of psoriasis vulgaris – Methods & evidence report. Available at: https://www.edf.one/home/Guidelines/EuroGuiDerm-psoriasis-vulgaris.html

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