Based on:
A Nast, C Smith, PI Spuls, G Avila Valle, Z Bata-Csörgö, H Boonen, E De Jong, I Garcia-Doval, P Gisondi, D Kaur-Knudsen, S Mahil, T Mäkönen, JT Maul, S Mburu, U Mrowietz, K Reich, E Remenyik, KM Rønholt, PG Sator, M Schmitt-Egenolf, M Sikora, K Strömer, O Sundnes, D Trigos, G Van Der Kraaij, N Yawalkar, C Dressler

The authors of this work have adapted, remixed, transformed, translated or built upon the pre-peer reviewed version of the following article: “EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris” by Nast A et al., which has been published in its final form at https://doi.org/10.1111/jdv.16915 and https://doi.org/10.1111/jdv.16926 and is also available at the European Dermatology Forum website (https://www.edf-one/home/Guidelines/EuroGuiDerm-psoriasis vulgaris.html), licensed under CC BY NC 4.0 (https://creativecommons.org/licenses/by-nc/4.0/). Adapted guidelines do not undergo an approval procedure by the European Dermatology Forum. This guideline has been approved by the German Dermatological Society and the Berufsverband der Deutschen Dermatologen e.V.
### Table 1: Decision grid (I) for the “conventional” treatment options and the expert assessment of their suitability in specific treatment circumstances.

| Specific circumstances | Conventional systemic agents | | | | | | |
|------------------------|-----------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|                       | Acitretin | Ciclosporin | Fumarates | Methotrexate | | | | | | | | | | | |
| Psoriatic arthritis | | | | | | | | | | | | | | | | |
| Chronic inflammatory bowel disease: Crohn’s disease | | | | | | | | | | | | | | | | |
| Chronic inflammatory bowel disease: ulcerative colitis | | | | | | | | | | | | | | | | |
| 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 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.

| Specific circumstances | Therapy | Small molecules | TNF inhibitors | Anti-IL12/23p40 | Anti-IL17 | Anti-IL23 |
|------------------------|---------|-----------------|----------------|-----------------|----------|----------|
| Psoriatic arthritis    | ↑↑      |                 |                |                 |          |          |
|                        |         |                 |                |                 |          |          |
|                        | ↑↑      |                 |                |                 |          |          |
| 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 | | | |
| Diabetes mellitus/ metabolic syndrome |             |                |                |                 |          |          |
| Dyslipidemia |             |                |                |                 |          |          |
| Advanced heart failure | ↑     |                | ↓↓             |                |          |          |
| Heart disease: ischemic heart disease |             |                |                |                |          |          |
| Latent / treated TB | ↑     |                | ↓↓             |                |          |          |
| Pregnancy |         |                |                |                |          | ↑        |

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.

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 German S3-Guideline on the treatment of Psoriasis vulgaris, adapted from EuroGuiDerm – Part 2

**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.

---

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, enthesal 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, enthesal and extra-articular musculoskeletal manifestations.

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.

**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).

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.

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.
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].

---

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) |
| 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 |

**Head-to-head comparisons**

| Placebo comparisons |
|----------------------|
| ETA 50 mg + MTX vs. MTX 20 mg QW | 3.35 | 2.24 to 4.99 | MODERATE | 0.67 | 0.50 to 0.89 | VERY LOW |
| INF 5 mg/kg W 0, 2, 6, 14 vs. PBO | 2.21 | 1.71 to 2.86 | MODERATE | 1.24 | 1.12 to 1.36 | LOW |
| IXE 80 mg Q2W vs. PBO | 1.23 | 1.05 to 1.41 | MODERATE | 1.05 | 0.90 to 1.23 | MODERATE |
| IXE 80 mg Q4W vs. PBO | 1.08 | 0.97 to 1.26 | MODERATE | 1.02 | 0.87 to 1.25 | MODERATE |
| MTX 7.5 mg QW vs. PBO | 1.02 | 0.97 to 1.07 | MODERATE | 1.03 | 0.97 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 150 mg Q4W 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 | 1.03 | 0.89 to 1.19 | MODERATE |
| UST 90 mg W 0, 4 and Q12W* vs. PBO | 2.26 | 1.80 to 2.82 | MODERATE | 0.96 | 0.75 to 1.24 | 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.
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.*

*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:*

**Crohn’s disease:** anti-TNF (infliximab, adalimumab, certolizumab) and anti-IL-12/23p40 (ustekinumab).

**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 oral treatment options in patients with psoriasis and IBD:

**Crohn’s disease:** anti-IL-23p19 (preferred risankizumab, guselkumab; also possible: tildrakizumab)

**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 targeted treatment options in patients with psoriasis and IBD:

**Crohn’s disease:** anti-IL-12p40 (infliximab, adalimumab, certolizumab) and anti-IL-12/23p40 (ustekinumab).
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 anti-rheumatic 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.

For patients with recent malignancy we recommend topical therapies, phototherapy (narrow band UVB)* and/or acitretin.
*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.

*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.

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].

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.

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 |

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.

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.

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 m² 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-hydroxy-methotrexate 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).

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.

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**

| Recommendation | Level of Evidence |
|----------------|-------------------|
| 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-HBeAg) 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. | Strong consensus, consensus-based |
| 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. | Strong consensus, consensus-based |

| Choice of treatment | Level of Evidence |
|---------------------|-------------------|
| 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) |
We recommend regular testing for HBsAG/HBV-DNA (e.g., every three months) during systemic treatment.\(^\uparrow\uparrow\) 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.\(^\uparrow\uparrow\) 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.\(^\uparrow\uparrow\) 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.

**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.

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.

Strong consensus, consensus-based

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.

We recommend against using these.

Strong consensus, consensus-based

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.

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.  

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.)

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.

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.

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*.

*EMA recommends six months as a means of precaution; the practice of the guideline group differs from this.

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.

Funding

The development of the EuroGuiDerm guideline was funded by the European Forum of Dermatology. The German adaptation was funded by the German Dermatological Society.

Conflict of interest

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

For authors of the Euro GuiDerm 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

Correspondence to

Prof. Dr. med. Alexander Nast, MD
Department of Dermatology, Venereology and Allergology
Division of Evidence-Based Medicine (dEBM)
Charité – Universitätsmedizin Berlin
Charitéplatz 1
10117 Berlin, Germany
E-mail: debm01@charite.de

References

1. Nast A, Gisondi P, Ormerod AD et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris – pdate 2015 – Short version – EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol 2015; 29: 2277–94.
2. Nast A, Spuls PI, van derKraaij G et al. European S3-Guideline on the systemic treatment of psoriasis vulgaris – Update Apreamilast and Secukinumab – EDF in cooperation with EADV and IPC. Journal of the European Academy of Dermatology and Venereology: JEDV 2017; 31: 1951–63.
3. Elmamoun M, Chandran V. Role of Methotrexate in the Management of Psoriatic Arthritis. Drugs 2018; 78: 611–9.
4. McInnes IB, Nash P, Ritchlin C et al. Secukinumab for psoriatic arthritis: comparative effectiveness versus licensed biologics/ apremilast: a network meta-analysis. J Comp Eff Res 2018; 7: 1107–23.
5. Mease PJ, Smolen JS, Behrens F et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis 2020; 79: 123–31.
6. Nash P, McInnes IB, Mease PJ et al. Secukinumab versus adalimumab for psoriatic arthritis: comparative effectiveness up to 48 weeks using a matching-adjusted indirect comparison. Rheumatol Ther 2018; 5: 99–122.
7. Dressler C, Eiser L, Pham PA, Nast A. Efficacy and safety of systemic treatments in psoriatic arthritis: a systematic review, meta-analysis and GRADE evaluation. J Eur Acad Dermatol Venereol 2019; 33: 1249–60.
8. Murashima A, Watanabe N, Ozawa N et al. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant’s serum. Ann Rheum Dis 2009; 68: 1793–4.
9. Gossec L, Smolen JS, Gaujoux-Viala C et al. European League Against Rheumatism recommendations for the management
of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis 2012; 71: 4–12.
10 Nast A, Amelunxen L, Augustin M et al. S3 Guideline for the treatment of psoriasis vulgaris, update – Short version part 2 – Special patient populations and treatment situations. J Dtsch Dermatol Ges 2018; 16: 806–13.
11 Amatore F, Villani AP, Tauber M et al. French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults. J Eur Acad Dermatol Venereol 2019; 33: 464–83.
12 Elmets CA, Leonardi CL, Davis DMR et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol 2019; 80: 1073–113.
13 Augustin M, Gaeske G, Radtke MA et al. Epidemiology and comorbidity of psoriasis in children. Br J Dermatol 2010; 162: 633–6.
14 Augustin M, Reich K, Gaeske G et al. Co morbidity and age-related prevalence of psoriasis: Analysis of health insurance data in Germany. Acta Derm Venereol 2010; 90: 47–51.
15 Targan SR, Feagan B, Vermeire S et al. A Randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe c rohn’s disease. Am J Gastroenterol 2016; 111: 1599–607.
16 Hueber W, Sands BE, Lewitzky S et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn’s disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut 2012; 61: 1693–700.
17 Armstrong A, Paul C, Puig L et al. Safety of ixekizumab treatment for up to 5 years in adult patients with moderate-to-severe psoriasis: results from greater than 17,000 patient-years of exposure. Dermatol Ther (Heidelb) 2020; 10(1): 133–50.
18 Whitlock SM, Enos CW, Armstrong AW et al. Management of psoriasis in patients with inflammatory bowel disease: From the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2018; 78: 383–94.
19 Feagan BG, Sandborn WJ, D’Haens G et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn’s disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet 2017; 389: 1699–709.
20 Feagan BG, Panes J, Ferrante M et al. Risankizumab in patients with moderate to severe Crohn’s disease: an open-label extension study. Lancet Gastroenterol Hepatol 2018; 3(10): 671–80.
21 Visvanathan S, Baum P, Salas A et al. Selective IL-23 inhibition by risankizumab modulates the molecular profile in the colon and ileum of patients with active Crohn’s disease: results from a randomised phase II biopsy sub-study. J Crohns Colitis 2018; 12: 1170–9.
22 Grossberg LB. A case report of successful treatment of crohn’s disease and psoriasis with guselkumab. Inflamm Bowel Dis 2019; 25: 684.
23 Berman HS, Villa NM, Shi VY, Hsiao JL. Guselkumab in the treatment of concomitant hidradenitis suppurativa, psoriasis, and Crohn’s disease. J Dermatol Treat 2019; 1–3.
24 Danese S, Neurath M, Kopon A et al. O PN60 Apremilast for active ulcerative colitis: a phase 2, randomised, double-blind, placebo-controlled induction study. J Crohns Colitis 2018; 12: S004–S04.
25 Patel V, Wang Y, MacDonald JK et al. Methotrexate for maintenance of remission in Crohn’s disease. Cochrane Database Syst Rev 2014; Cd006684.
26 McDonald JW, Wang Y, Tsoulis DJ et al. Methotrexate for induction of remission in refractory Crohn’s disease. Cochrane Database Syst Rev 2014: Cd003459.
27 Chande N, Wang Y, MacDonald JK, McDonald JW. Methotrex ate for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2014: Cd006618.
28 Herfarth H, Barnes EL, Valentine JF et al. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. Gastroenterology 2018; 155: 1098–108.e9.
29 Melo FJ, Magina S. Clinical management of Anti-TNF-alpha-induced psoriasis or psoriasisiform lesions in inflammatory bowel disease patients: a systematic review. Int J Dermatol 2018; 57: 1521–32.
30 Laharie D, Bourreille A, Branche J et al. Long-term outcome of patients with steroid-refractory acute severe UC treated with ciclosporin or infliximab. Gut 2018; 67: 237–43.
31 Peleva E, Exton LS, Kelley K et al. Risk of cancer in patients with psoriasis on biological therapies: a systematic review. Br J Dermatol 2018; 178: 103–11.
32 Vaengebjerg S, Skov L, Egeberg A, loft ND. prevalence, incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. JAMA Dermatol 2020; 156(4): 421–9.
33 Garcia-Doval I, Hernandez MV, Vanaclocha F et al. Should tumour necrosis factor antagonist safety information be applied from patients with rheumatoid arthritis to psoriasis? Rates of serious adverse events in the prospective rheumatoid arthritis BIOBADASER and psoriasis BIOBADADERM cohorts. Br J Dermatol 2017; 176: 643–9.
34 HoIroyd CR, Seth R, Bukhari M et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Rheumatology (Oxford) 2019; 58: 63–642.
35 Luo X, Deng C, Fei Y et al. Malignancy development risk in psoriatic arthritis patients undergoing treatment: A systematic review and meta-analysis. Semin Arthritis Rheum 2019; 48: 626–31.
36 Kim SC, Schneweiss S, Liu J et al. Biologic disease-modifying antirheumatic drugs and risk of high-grade cervical dysplasia and cervical cancer in rheumatoid arthritis: a cohort study. Arthritis Rheum 2016; 68: 2106–13.
37 Mercer LK, Low AS, Galloway JB et al. Anti-TNF therapy in women with rheumatoid arthritis with a history of carcinoma in situ of the cervix. Ann Rheum Dis 2013; 72: 143–4.
38 Micic D, Komaki Y, Alavanja A et al. Risk of cancer recurrence among individuals exposed to antitumor necrosis factor therapy: a systematic review and meta-analysis of observational studies. J Clin Gastroenterol 2019; 53: e1–e11.
39 Scott FI, Mamtani R, Brensinger CM et al. Risk of nonmela noma skin cancer associated with the use of immunosuppres sant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. JAMA Dermatol 2016; 152: 164–72.
Shelton E, Laharie D, Scott Fi et al. Cancer recurrence following immune-suppressive therapies in patients with immune-mediated diseases: a systematic review and meta-analysis. Gastroenterology 2016; 151: 97–109.e4.

Cohen BE, Martires KJ, Ho RS. Psoriasis and the risk of depression in the US population: national health and nutrition examination survey 2009–2012. JAMA Dermatol 2016; 152: 73–9.

Egeberg A, Thyssen JP, Wu JJ, Skov L. Risk of first-time and recurrent depression in patients with psoriasis: a population-based cohort study. Br J Dermatol 2019; 180: 116–21.

Fleming P, Roubille C, Richer V et al. Effect of biologics on depressive symptoms in patients with psoriasis: a systematic review. J Eur Acad Dermatol Venereol 2015; 29: 1063–70.

Tribo MJ, Turroja M, Castano-Vinyals G et al. Patients with moderate to severe psoriasis associate with higher risk of depression and anxiety symptoms: results of a multivariate study of 300 Spanish individuals with psoriasis. Acta Derm Venereol 2019; 99: 417–22.

Abbott R, Whear R, Nikolau V et al. Tumour necrosis factor-alpha inhibitor therapy in chronic physical illness: A systematic review and meta-analysis of the effect on depression and anxiety. J Psychosom Res 2015; 79: 175–84.

Carrascosa JM, Rebollo F, Gomez S, De-la-Cueva P. Effects of etanercept on the patient-perceived results (PROs) in patients with moderate-to-severe plaque psoriasis: systematic review of the literature and meta-analysis. J Dermatolog Treat 2018; 29: 806–11.

Gordon KB, Armstrong AW, Han C et al. Anxiety and depression in patients with moderate-to-severe psoriasis and comparison of change from baseline after treatment with guselkumab vs. adalimumab: results from the Phase 3 VOYAGE 2 study. J Eur Acad Dermatol Venereol 2018; 32: 1940–9.

Griffiths CEM, Fava M, Miller AH et al. Impact of ixekizumab treatment on depressive symptoms and systemic inflammation in patients with moderate-to-severe psoriasis: an integrated analysis of three phase 3 clinical studies. Psychother Psychosom 2017; 86: 260–7.

Schmieder A, Poppe M, Hametner C et al. Impact of fumaric acid esters on cardiovascular risk factors and depression in psoriasis: a prospective pilot study. Arch Dermatol Res 2015; 307: 413–24.

Kim SJ, Park MY, Pak K et al. Improvement of depressive symptoms in patients with moderate-to-severe psoriasis treated with ustekinumab: an open label trial validated using beck depression inventory, Hamilton depression rating scale measures and (18)fluorodeoxyglucose (FDG) positron emission tomography (PET). J Dermatolog Treat 2018; 29: 761–8.

Arican O, Sasmaz S, Ozbulut O. Increased suicidal tendency in a case of psoriasis vulgaris under acitretin treatment. J Eur Acad Dermatol Venereol 2006; 20: 464–5.

Henderson CA, Highet AS. Depression induced by etretinate. BMJ 1989; 298: 964.

Hayes J, Koo J. Depression and acitretin: a true association or a class labeling? J Drugs Dermatol 2011; 10: 409–12.

Starling J 3rd, Koo J. Evidence based or theoretical concern? Pseudotumor cerebri and depression as acitretin side effects. J Drugs Dermatol 2005; 4: 690–6.

European Medicines Agency. Retinoid-containing medicinal products. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/retinoid-containing-medicinal-products [Last accessed May 20, 2021].

European Medicines Agency. Acitretin SmPC and Patient Leaflet. Available from: https://www.medicines.org.uk/emc/product/10247/smpc [Last accessed May 20, 2021].

Lebwohl M, Strober B, Menter A et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. New Engl J Med 2015; 373: 1318–28.

Papp KA, Reich K, Paul C et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol 2016; 175: 273–86.

Beck KM, Koo J. Brodalumab for the treatment of plaque psoriasis: up-to-date. Expert Opin Biol Ther 2019; 19: 287–92.

European Medicines Agency. Kyntheum SmPC and Patient Leaflet. Available from: https://www.ema.europa.eu/en/documents/product-information/kyntheum-epar-product-information_en.pdf [Last accessed May 20, 2021].

Crowley J, Thaci D, Joly P et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥ 156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). J Am Acad Dermatol 2017; 77: 310–7 e1.

Kavanaugh A, Gladman DD, Edwards CJ et al. Long-term experience with apremilast in patients with psoriatic arthritis: 5-year results from a PALACE 1–3 pooled analysis. Arthritis Res Ther 2019; 21: 118.

European Medicines Agency. Otezla (apremilast): New important advice regarding suicidal ideation and behaviour. Celgene Europe Limited 2016.

European Medicines Agency. Otezla SmPC and Patient Leaflet. Available from: https://www.medicines.org.uk/emc/product/10709/smpc [Last accessed May 20, 2021].

Dehpouri T, Rokni GR, Narenjbon NA et al. Evaluation of the glycemic effect of methotrexate in psoriatic arthritis patients with metabolic syndrome: A pilot study. Dermatology re- ports 2019; 11: 29565.

Owczarczyk-Saczzonek A, Drozdowski M, Maciejewskas-Radomska A et al. The effect of subcutaneous methotrexate on markers of metabolic syndrome in psoriatic patients – preliminary report. Postepy dermatologii i alergologii 2018; 35: 53–9.

Wu JJ, Liu L, Asgari MM et al. Initiation of TNF inhibitor therapy and change in physiologic measures in psoriasis. J Eur Acad Dermatol Venereol 2014; 28: 1380–7.

Rosenberg P, Urwitz H, Johannesson A et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. J Hepatol 2007; 46: 1111–8.

Singh JA, Guyatt G, Ogdie A et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Care Res (Hoboken) 2019; 71: 2–29.

Gisondi P, Cazzaniga S, Chimenti S et al. Metabolic abnormalities associated with initiation of systemic treatment for psoriasis: evidence from the Italian Psocare Registry. J Eur Acad Dermatol Venereol 2013; 27: 30–41.
85 Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37: 2315–81.
86 Mach F, Baigent C, Catapano AL et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41: 111–88.
87 Aksettijewich M, Lateef SS, Anzenberg P et al. Chronic inflammation, cardiometabolic diseases and effects of treatment: Psoriasis as a human model. Trends Cardiovasc Med 2020; 30: 472–8.
88 Chen S, Crother TR, Arditi M. Emerging role of IL-17 in atherosclerosis. J Innate Immun 2010; 2: 325–33.
89 vanStebut E, Reich K, Thaçi D et al. Impact of secukinumab on endothelial dysfunction and other cardiovascular disease parameters in psoriasis patients over 52 weeks. J Invest Dermatol 2019; 139: 1054–62.
90 Elnabawi YA, Dey AK, Goyal A et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. Cardiovasc Res 2019; 115: 271–8.
91 Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Revista espanola de cardiologia (English ed). 2016; 69: 1167.
92 Wan J, Wang S, Haynes K et al. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. BMJ 2013; 347: f5961.
93 Garcia-Doval I, Carretero G, Vanaclocha F et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch Dermatol 2012; 148: 463–70.
94 Chimenti MS, Gramiccia T, Saraceno R et al. Apremilast for the treatment of psoriasis. Expert Opin Pharmacother 2015; 16: 2083–94.
95 Cada DJ, Levien TL, Baker DE. Dimethyl fumarate. Hosp Pharm 2013; 48: 668–79.
96 Rostami-Yazdi M, Clement B, Mrowietz U. Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients. Arch Dermatol Res 2010; 302: 531–8.
97 Rostami-Yazdi M, Clement B, Schmidt TJ et al. Detection of metabolites of fumaric acid esters in human urine: implications for their mode of action. J Invest Dermatol 2009; 129: 231–4.
98 Maza A, Montaudie H, Sibidian E et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venerool 2011; 25 (Suppl 2): 19–27.
99 Issa N, Kukla A, Ibrahim HN. Calcineurin inhibitor nephrotoxicity: a review and perspective of the evidence. Am J Nephrol 2013; 37: 602–12.
100 Kremer JM, Petrillo GF, Hamilton RA. Pharmacokinetics and renal function in patients with rheumatoid arthritis receiving a standard dose of oral weekly methotrexate: association with significant decreases in creatinine clearance and renal clearance of the drug after 6 months of therapy. J Rheumatol 1995; 22: 38–40.
101 Ebers GC, Bulman DE, Sadovnick AD et al. A population-based study of multiple sclerosis in twins. N Engl J Med 1986; 315: 1638–42.
102 Siva A. Asymptomatic MS. Clin Neurol Neurosurg 2013; 115(Suppl 1): S1–5.

103 Tang KT, Chen YM, Chang SN et al. Psoriatic patients with chronic viral hepatitis do not have an increased risk of liver cirrhosis despite long-term methotrexate use: Real-world data from a nationwide cohort study in Taiwan. J Am Acad Dermatol 2018; 79: 672–8.

104 Lewinsohn DM, Leonard MK, LoBue PA et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of tuberculosis in adults and children. Clin Infect Dis 2017; 64: 111–5.

105 World Health Organization. WHO Guidelines Approved by the Guidelines Review Committee. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization World Health Organization 2018.

106 Golden MP, Vikram HR. Extrapulmonary tuberculosis: a systematic review. Am J Med 1977; 63: 410–20.

107 Simon HB, Weinstein AJ, Pasternak MS et al. Genitourinary tuberculosis. Clinical features in a general hospital population. Medicine (Baltimore) 1974; 53: 377–90.

108 Christensen WI. Genitourinary tuberculosis: review of 102 cases. Medicine (Baltimore) 2011; 90: e24.

109 Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician 2005; 72: 1761–8.

110 National Collaborating Centre for Chronic Conditions (UK); Centre for Clinical Practice at NICE (UK). Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: National Institute for Health and Clinical Excellence (UK); 2011. PMID: 22720337.

111 Doherty SD, Van Voorhees A, Lebwohl MG et al. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol 2008; 59: 209–17.

112 Arias-Guillen M, Sanchez Menendez MM, Alperi M et al. High rates of tuberculin skin test positivity due to methotrexate therapy: False positive results? Semin Arthritis Rheum 2018; 48: 536–46.

113 Papp KA, Griffiths CE, Gordon K et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol 2013; 168: 844–54.

114 Cantini F, Nannini C, Niccoli L et al. Risk of tuberculosis reactivation in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis receiving non-anti-TNF-targeted biologics. Mediators Inflamm 2017; 2017: 8909834.

115 Snait I, Bercovici E, Solomon-Cohen E et al. Active tuberculosis in patients with psoriasis receiving biologic therapy: a systematic review. Am J Clin Dermatol 2019; 20: 483–91.

116 Boyd AS, Morris LF, Phillips CM, Menter MA. Psoriasis and pregnancy: hormone and immune system interaction. Int J Dermatol 1996; 35: 169–72.

117 Bobotis R, Gulliver WP, Monaghan K et al. Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies. Br J Dermatol 2016; 175: 464–72.

118 Yang Y-W, Chen C-S, Chen Y-H, Lin H-C. Psoriasis and pregnancy outcomes: a nationwide population-based study. J Am Acad Dermatol 2011; 64: 71–7.

119 Lima XT, Janakiraman V, Hughes MD, Kimball AB. The impact of psoriasis on pregnancy outcomes. J Invest Dermatol 2012; 132: 85–91.

120 Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol 2009; 104: 228–33.

121 Malek A, Sager R, Kuhn P et al. Evolution of maternofetal transport of immunoglobulins during human pregnancy. Am J Reprod Immunol 1996; 36: 248–55.

122 Pottinger E, Woolf RT, Exton LS et al. Exposure to biological therapies during conception and pregnancy: a systematic review. Br J Dermatol 2018; 178: 95–102.

123 Ferrante M, Vermeire S, Rutgeerts PJ. Drug safety evaluation of certolizumab pegol. Expert Opin Drug Saf 2014; 13: 255–66.

124 Mahadevan U, Wolf DC, Dubinsky M et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013; 11(3): 286–92; quiz e24.

125 Mariette X, Förger F, Abraham B et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis 2018; 77: 228–33.

126 Clouse ME, Förger F, Hwang C et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis 2017; 76: 1890–6.

127 Carman WJ, Accortt NA, Anthony MS et al. Pregnancy and infant outcomes including major congenital malformations among women with chronic inflammatory arthritis or psoriasis, with and without etanercept use. Pharmacoepidemiol Drug Saf 2017; 26: 1109–18.

128 Burmester GR, Landewé R, Genovese MC et al. Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis. Ann Rheum Dis 2017; 76: 414–7.

129 Bröms G, Granath F, Stephansson O, Kieler H. Preterm birth in women with inflammatory bowel disease – the association with disease activity and drug treatment. Scand J Gastroenterol 2016; 51: 1462–9.

130 Bröms G, Granath F, Ek bom A et al. Low risk of birth defects for infants whose mothers are treated with anti-tumor necrosis factor agents during pregnancy. Clin Gastroenterol Hepatol 2016; 14(2): 234–41.e1–5.

131 Luu M, Benzenine E, Doret M et al. Continuous anti-TNFα use throughout pregnancy: possible complications for the mother but not for the fetus. A retrospective cohort on the French National Health Insurance Database (EVASION). Am J Gastroenterol 2018; 113(1): 1669–77.

132 Casanova MJ, Chaparro M, Domenech E et al. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol 2013; 108(3): 433–40.
Cooper WO, Cheetham TC, Li D-K et al. Brief report: Risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. Arthritis Rheumatol 2014; 66(2): 444–50.

Weber-Schoendorfer C, Oppermann M, Wacker E et al. Pregnancy outcome after TNF-α inhibitor therapy during the first trimester: a prospective multicentre cohort study. Br J Clin Pharmacol 2015; 80: 727–39.

Diav-Citrin O, Ocheretianski-Volodarsky A, Shechtman S, Ornoy A. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reprod Toxicol 2014; 43: 78–84.

Schnitzler F, Fidder H, Ferrante M et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. Inflamm Bowel Dis 2011; 17: 1846–54.

Seirafi M, deVroey B, Amiot A et al. Factors associated with pregnancy outcome in anti-TNF treated women with inflammatory bowel disease. Aliment Pharmacol Ther 2014; 40: 163–73.

Verstappen SMM, King Y, Watson KD et al. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011; 70: 823–6.

Clowse MEB, Schuerle AE, Chambers C et al. Pregnancy outcomes after exposure to certolizumab pegol: updated results from a pharmacovigilance safety database. Arthritis Rheumatol 2018; 70: 1399–407.