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GUIDELINES

EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris – Part 2: specific clinical and comorbid situations

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Abstract

This evidence- and consensus-based guideline on the treatment of psoriasis vulgaris was developed following the EuroGuiDerm Guideline and Consensus Statement Development Manual. The second part of the guideline provides guidance for specific clinical and comorbid situations such as treating psoriasis vulgaris patient with concomitant psoriatic arthritis, concomitant inflammatory bowel disease, a history of malignancies or a history of depression or suicidal ideation. It further holds recommendations for concomitant diabetes, viral hepatitis, disease affecting the heart or the kidneys as well as concomitant neurological disease. Advice on how to screen for tuberculosis and recommendations on how to manage patients with a positive tuberculosis test result are given. It further covers treatment for pregnant women or patients with a wish for a child in the near future. Information on vaccination, immunogenicity and systemic treatment during the COVID-19 pandemic is also provided.

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The guideline was developed by all co-authors. The EuroGuiDerm Team[1] coordinated the work.

Conflicts of Interest

The guideline development group consists of 25 experts from 14 countries, seven of which declared to have personal–financial conflict of interests, which is a total of 28% of the group members (see Table 1 of the Methods & Evidence Report). The EuroGuiDerm Team does not have any personal–financial conflict of interests to disclose regarding the subject at hand.

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I. Notes on use/Disclaimer

The EuroGuiDerm guideline on the systemic treatment of psoriasis vulgaris was developed in accordance with the EuroGuiDerm Methods Manual v1.3, which can be found on the website of the European Dermatology Forum (EDF), subsection EuroGuiDerm/EDF Guidelines https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html.

VIII Methods Section

(section identical to part 1 of the guideline)

For the detailed description of the guideline development process, please see supplementary material.

In short, the guideline development group is comprised of 23 dermatology experts from 14 countries, two patient representatives nominated by IFPA and the EuroGuiDerm methodologists. Twenty-eight per cent declared personal–financial conflicts of interests (no vote/count). The guideline draft texts and recommendations were developed by the experts in working groups, reviewed, discussed and amended where appropriate by the entire group. All texts and recommendations were voted on with a minimal agreement of >50%. Structured consensus techniques were used during all three online consensus conferences.

Wording as suggested by the GRADE Working Group to standardize the wording of all recommendations was used,[1] see below.

Wording of recommendations[2–5]

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'We recommend . . .'	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision-making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Weak recommendation **for** the use of an intervention	'We suggest . . .'	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
No recommendation with respect to an intervention	'We cannot make a recommendation with respect to . . .'	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence data available, conflicting outcomes, etc.)
Weak recommendation **against** the use of an intervention	'We suggest against . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation **against** the use of an intervention	'We recommend against . . .'	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

The recommendations are presented throughout this guideline as displayed below: first the content, then the arrows and colours indicating the direction and the strength of the recommendations, respectively, and lastly the rate of expert agreement (consensus strength). Evidence-based recommendations are indicated as such.

IX. Main Recommendations

The EuroGuiDerm guideline development group considers the time a treatment has been available a relevant factor when considering different treatment options (Tables 1 and 2).

We **recommend** to do tuberculosis screening according to local regulations.	↑↑	Strong consensus[1] 100% agreement Expert consensus

[1]due to personal-financial conflict of interest x abstentions

The main recommendations (Part 1) are based on the Cochrane review.[6] The tables 'Instruction for use' and 'lab controls' have also been voted on – these are consensus-based. The rate of expert agreement is displayed too.

An internal and external review was conducted. Dissemination, implementation and monitoring plans were developed as well as a joint Q&A section for patients. For more details, see methods and evidence report.

3 Guidance for specific clinical and comorbid situations

3.1. 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.[7,8] An existing systematic review and meta-analysis were updated, details of which can be found in the Methods and Evidence report.

Table 1 Overview of 'conventional' treatment options and the expert assessment of their suitability in specific treatment circumstances (decision grid I)

Specific circumstances \ Therapy	Conventional systemic agents			
	Acitretin	Ciclosporin	Fumarates	Methotrexate
Concomitant psoriatic arthritis				↑↑ peripheral active joint involvement
Chronic inflammatory bowel disease: Crohn's Disease	↑ especially cases with mild paradoxical psoriasis			↑ 2nd choice oral treatment
Chronic inflammatory bowel disease: Ulcerative colitis	↑ especially cases with mild paradoxical psoriasis	↑ 2nd choice oral treatment		
Diabetes mel./metabolic syndrome		↓		↓
Dyslipidaemia	↓			
Advanced heart failure	↑	↓		↑
Heart Disease: Ischemic heart disease		↓		↑
Concomitant latent / treated TB	↑		↑	
Pregnancy	↓↓	↑ preferred conventional	↓	↓↓

Symbols	Implications[1]
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
	See background text and specific recommendations
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.

[1]Adapted from GRADE

Table 2 Overview of 'biologics' treatment options and the expert assessment of their suitability in specific treatment circumstances (decision grid II)

Therapy / Specific circumstances	Small molecules	TNF inhibitors				Anti-IL12/23	Anti-IL17			Anti-IL23		
	Apremilast	Etanercept	Infliximab	Adalimumab	Certolizumab	Ustekinumab	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Tildrakizumab	Risankizumab
Concomitant 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 mel./ metabolic syndrome												
Dyslipidaemia												
Advanced heart failure	↑	↓↓						↑				
Heart Disease: Ischemic heart disease		↑										
Concomitant latent / treated TB	↑	↓↓						↑				
Pregnancy	↓				↑ preferred choice biologic							

Symbols	Implications[2]
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
	See background text and specific recommendations
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.

[2]Adapted from GRADE

Results/Answer[9–12]

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[1] 100% agreement EXPERT CONSENSUS

[1]Due to personal–financial conflict of interest 4 abstentions

Treatments are usually categorized as NSAIDs (e.g. diclofenac), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), e.g. MTX, targeted synthetic (ts)DMARDS (e.g. apremilast) and biological (b)DMARDs (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 RCT data on psoriatic arthritis.

Table 3 Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al.[13] updated, see methods 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 50mg + MTX vs. MTX 20mg QW	1.28	1.11 to 1.48	LOW	1.01	0.92 to 1.11	MODERATE
INF 5mg/kg W 0, 2, 6, 14 + MTX vs. MTX 15mg QW	1.40	1.07 to 1.84	VERY LOW	1.65	1.08 to 2.52	VERY LOW
IXE 80mg Q2W vs. ADA 40mg Q2W	1.08	0.86 to 1.36	LOW	1.02	0.83 to 1.25	MODERATE
IXE 80mg Q4W vs. ADA 40mg Q2W	0.96	0.86 to 1.06	LOW	1.14	1.01 to 1.28	VERY LOW
Placebo comparisons						
ADA 40mg EOW vs. PBO	3.35	2.24 to 4.99	MODERATE	0.67	0.50 to 0.89	VERY LOW
APR 30mg BID vs. PBO	1.94	1.59 to 2.38	MODERATE	1.24	1.12 to 1.36	LOW
APR 20mg BID vs PBO	1.86	1.49 to 2.31	MODERATE	1.27	1.15 to1.41	LOW
CZP 400mg Q4W vs. PBO	2.36	1.68 to 3.31	MODERATE	1.05	0.90 to 1.23	MODERATE
CZP 200mg Q2W vs. PBO	2.71	1.95 to 3.76	MODERATE	1.01	0.86 to 1.19	MODERATE
ETA 25mg BIW vs. PBO	4.05	2.56 to 6.40	LOW	n.d.		
INF 5mg/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 80mg Q2W vs. PBO	2.21	1.71 to 2.86	MODERATE	1.39	1.09 to 1.78	LOW
IXE 80mg Q4W vs. PBO	2.25	1.59 to 3.18	MODERATE	1.41	1.10 to 1.79	LOW
MTX 7.5mg QW vs. PBO	1.82	0.97 to 3.40	LOW	n.d.		
SEC 150mg Q4W vs. PBO	2.44	2.10 to 2.84	HIGH	1.03	0.95 to 1.12	HIGH
SEC 150mg Q4W + LD vs. PBO	2.06	1.70 to 2.49	HIGH	1.01	0.89 to 1.15	MODERATE
SEC 300mg Q4W + LD vs. PBO	2.28	1.87 to 2.80	MODERATE	1.02	0.89 to 1.16	MODERATE
UST 45mg W 0, 4 and Q12W vs PBO	1.95	1.52 to 2.50	HIGH	n.d.		
UST 90mg W 0, 4 and Q12W* vs PBO	2.26	1.80 to 2.82	MODERATE	0.96	0.75 to1.24	VERY LOW

Abbreviations: 95% CI, 95% confidence interval; ACR20, 20% improvement in American College of Rheumatology response criteria; ADA, adalimumab; APR, apremilast; BID, twice a day; BIW, twice a week; CZP, certolizumab pegol; EOW, every other week; ETA, etanercept; INF, infliximab; kg, kilograms IXE, ixekizumab; LD, loading dose; mg, milligrams; MTX, methotrexate; PBO, placebo; Q12W, every 12 weeks; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once a week; RR, risk ratio; Sec, secukinumab; UST, ustekinumab; W, week.

*One study (Gottlieb et al. 2009) reported induction dose of QW (weeks 0–3).

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 involvement. Treatment of NSAIDs should be limited to the lowest required dosage for the shortest period as needed.[14]

Conventional synthetic DMARDs (e.g. MTX).

MTX 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.[14]

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, or glucocorticoid site injections if applicable and/or potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, and extra-articular musculoskeletal manifestations.	↑↑	Strong consensus 100% agreement EVIDENCE AND EXPERT CONSENSUS Table 3

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 100% agreement EXPERT CONSENSUS

For inadequately responding patients after at least one synthetic DMARD, we **recommend** the use of biological DMARDs as monotherapy or in combination with synthetic DMARDs.	↑↑	Strong consensus[1] 100% agreement EVIDENCE AND EXPERT CONSENSUS 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 100% agreement EXPERT CONSENSUS

[1]Due to personal–financial conflict of interest 4 abstentions

Biological DMARDs.

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 and the IL-17A antibody treatments might be equally effective; however, more data are needed for its real-life long-term efficacy, safety and comedication.

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

Other treatment options. As apremilast is less efficacious than bDMARDs, it is suggested for patients with concomitant psoriatic arthritis and 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 and in entheseal areas (enthesitis).

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'.[15]. Tapering of glucocorticoids should be done slowly and stepwise when feasible.

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

Narrative review of the existing literature and an assessment of approval status of psoriasis therapies for Crohn's disease and ulcerative colitis were conducted. Existing guidelines were consulted.[16–18]

Results/Answer

Likely due to an overlap in the pathophysiology and genetic background of psoriasis and Crohn's disease, the risk of psoriasis

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[1] 100% agreement EXPERT CONSENSUS
In patients with psoriasis and active IBD or a history of IBD, we **recommend** to preferentially use 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 targeted 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 oral treatment options in patients with psoriasis and IBD *Crohn's disease*: Methotrexate *Active ulcerative colitis*: Ciclosporine (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	↑	
We **suggest against** the use of anti IL 17 antibodies in patients with inflammatory bowel disease.	↓	

[1]Due to personal-financial conflict of interest 4 abstentions

patients developing Crohn's disease is approximately two- to threefold higher compared to the general population.[19,20]

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.[21,22] 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.[23] In a recent summary of the safety observed in clinical trials of secukinumab in psoriasis, for example, the event rate per 100 patient-years of exposure was 0.05 (95% confidence interval 0.02–0.1) for Crohn's disease (approximately one case per 2000 patients treated for one year) and 0.1 (0.07–0.2) for ulcerative colitis (approximately one case per 1000 patients treated for one year).[24] Since anti-TNF antibodies and ustekinumab, and possibly anti-IL-23 antibodies, are effective in treating Crohn's disease,[25] the use of these biologics in psoriasis may decrease the occurrence of new-onset Crohn's disease cases in psoriasis patients.[26]

The prescription information for secukinumab and ixekizumab include a warning regarding the use of these drugs in patients with inflammatory bowel disease, while active Crohn's disease is a contraindication for the use of brodalumab.

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. Notably, the anti-TNF fusion protein etanercept failed in clinical trials in Crohn's disease (reviewed in Whitlock SM et al. 2018[27]).

There is an ongoing phase II/III clinical development programme 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[25,28] and are supported by immunological findings in the intestinal mucosa of patients with Crohn's disease receiving the drug.[29] There are several published case reports on the successful use of guselkumab in patients with Crohn's disease.[30,31]

Due to their intestinal side-effect profile with a relatively frequent induction of abdominal pain, loose stools and diarrhoea, fumarates should not be used in patients with inflammatory bowel disease. 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 2 trial with ulcerative colitis.[32]

Methotrexate has limited efficacy in Crohn's disease[33,34] and probably even less in ulcerative colitis,[35,36] 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.[37]

Ciclosporin is frequently used in the treatment of steroid-refractory ulcerative colitis and has demonstrated long-term outcomes similar to those of infliximab.[38]

3.3 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.[7,8] A systematic search was conducted, details of which can be found in the Methods & Evidence Report.

Results/Answer Theoretically, immunomodulatory therapies used for psoriasis have the potential to affect the course of a malignant disease, and the safety of using them in this context is uncertain.

In clinical practice, different scenarios are associated with different risks and the answer might not be the same for each of them. Patients can present with precancer (such as cervical dysplasia, colonic polyps or Barrett's oesophagus), low risk cancer (NMSC, cancer with a long period of non-recurrence, usually defined as more than 5 years) or high-risk cancer (active cancer, recent aggressive cancer).

Available evidence to guide clinicians in these situations is scarce. Patients with malignancies are excluded from randomized clinical trials, so RCTs will not provide valid answers. Information about patients with previous cancer can only come from observational studies, which are less valid, as they are commonly affected by confounding by indication. There are techniques that can help control for this type of confounding, but these kinds of analyses require large numbers of patients that are difficult to enrol. This power issue is the reason for results usually being given for different cancers merged and also for different drugs grouped.

Most of the data available is of marginal relevance to this question:

Overall risk of cancer in psoriasis Psoriasis is associated with increased mortality due to many diseases, including an increased risk of cancer. It is not clear whether this is due to the disease itself, or is influenced by lifestyle factors (mainly alcohol and smoking) or therapy.[39]

A recent systematic review and meta-analysis of 112 observational cohort studies of patients with psoriasis and psoriatic arthritis revealed a slightly increased risk of several cancer types, particularly keratinocyte cancer and lymphoma.[40]

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 of 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.[41] Vaengebjerg et al did not find increased risk of cancer in patients with psoriasis and psoriatic arthritis on biologics compared with other systemic therapies.[40]

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.[42]

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.[43] Luo et al, analysing 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 NMSC and included studies have not considered the likely effect of previous PUVA therapy.[44] SmPCs of TNF inhibitors contain information regarding the risk of lymphoma/leukaemia. However, these are rare events and data supporting this association are conflicting. So far no such association have been shown for psoriasis patients.[41]

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) describes that initiation of therapy with a biological disease-modifying antirheumatic 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.[45] Conversely, a review analysing 238 women with RA and a history of cervical carcinoma in situ, no genital cancer was observed in the TNFi-treated group over a median of 5.2 years of follow-up compared with two incidents of genital cancer in the bDMARD-treated group, during a median follow-up of 3.9 years.[46]

A systematic review 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 non-biologic disease-modifying antirheumatic drugs (DMARD), 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 nbDMARD.[47]

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

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[1] 100% agreement EXPERT CONSENSUS
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** to discuss 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 non melanoma 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, ustekinumab can be used based on existing safety data on a case-by-case basis including discussion with cancer specialist. We **suggest** anti-IL17, 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.	↑	

[1]Due to personal-financial conflict of interest 3 abstentions

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).[48]

Another systematic review analysed 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 1698 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 were higher among patients receiving combination immune suppression.[49]

French guidelines have reviewed the risk of cancer associated with systemic therapies. Ciclosporine has been clearly linked to an increased risk of cancer and a recommendation to avoid it has been issued. Evidence from larger patient cohort over long periods of time on the risk of the newer drugs such as the anti-IL-17, anti-23 antibodies and apremilast is still very scarce.[17] From a theoretical point of view, acitretin has lower efficacy but might also have the lowest risk in these patients. Phototherapy is associated with skin cancer, but not with other cancers. Although evidence is not strong, there does not seem to be a difference in risk with methotrexate and anti-TNFs, except for a possible increase in risk of NMSC for methotrexate.[17]

3.4 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.[7,8] A systematic search was conducted, details of which can be found in the Methods & Evidence report.

Results/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.[18,50–53] 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.[52,54–59] In a head-to-head study, guselkumab was associated with greater improvements in symptoms of depression compared with adalimumab.[56] In a prospective, longitudinal registry study, biologic therapy was found to have the greatest improvement on symptoms of depression followed by conventional systemic therapy and phototherapy.[18,60] Taken together, these data suggest that the more effective the intervention for psoriasis, the greater the benefit to the mood. However, whether the overall beneficial effect on depressive symptoms is direct, or indirect (through improvement in psoriasis and therefore mood) is not clear.

Systemic treatments for psoriasis with special attention to a possible increased risk of depression, suicide ideation and completed suicide are discussed below:

Acitretin: Acitretin has been reported to be associated with depression in some case reports.[61,62] 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.[63,64] A formal review of retinoids (including acitretin and isotretinoin) carried out by EMA's Pharmacovigilance Risk Assessment Committee in 2018[65] 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.[66] 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).[67,68] An expert opinion (2019) discussing these observed cases of suicide highlighted the following aspects[69]: 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 centre. Both symptoms of depression and anxiety decreased during treatment with brodalumab.[68]

In the European SmPC, the reported suicidal ideation and behaviour, 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 behaviour 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 behaviour

is identified, it was recommended to discontinue treatment with brodalumab.[70]

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.[71] 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.[72] Postmarketing 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 European Medicines Agency and the Health Products Regulatory Authority in 2016.[73] In here, it was stated that evidence from clinical trials and postmarketing experience suggested a causal association between suicidal ideation and behaviour with the use of apremilast. The SmPC and patient leaflet for apremilast were updated to add a warning about depression (common adverse reaction (≥1/100 to <1/10)) and suicidal behaviour and ideation (uncommon adverse reaction (≥1/1000 to <1/100)).[74]

It was recommended that risks and benefits of starting or continuing treatment with apremilast should be carefully assessed in patients with previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events are in use or intended. Additionally, it was recommended to discontinue treatment with apremilast in patients suffering from new or worsening psychiatric symptoms, or if suicidal ideation or suicidal attempt is identified.

Moderate-to-severe psoriasis is commonly accompanying with metabolic disorders including type 2 diabetes mellitus, obesity, dyslipidaemia, nonalcoholic fatty liver disease and metabolic syndrome.[75] In particular, several meta-analyses confirmed the association between psoriasis and diabetes as well as the new AAD guidelines[18,75-77] Amstrong et al.[75] found that psoriasis had an odds ratio (OR) of 1.59 (95% CI, 1.38–1.83) for diabetes. The pooled OR was 1.53 (95% CI, 1.16–2.04) for mild psoriasis and 1.97 (95% CI, 1.48–2.62) for severe psoriasis. A nationwide population-based cohort study involving 14 158 adults with psoriasis confirmed that the risk of diabetes in psoriatic patients is correlated to the severity of psoriasis.[78] The association between psoriasis and diabetes could be explained considering a common genetic background, insulin resistance and the unhealthy lifestyles such as overeating and sedentary life, which are common in patients with psoriasis.[79]

In addition, there is a strong association between psoriasis and obesity which induces itself insulin resistance.[80] Obesity itself is a significant risk factor to develop type 2 diabetes[18]. Systemic treatments for psoriasis could also impair glucose homeostasis and/or other metabolic parameters, especially in case of continuous and prolonged use. Short-term treatment with methotrexate does not appear to have a negative effect on carbohydrate metabolism parameters in patients with psoriasis or psoriatic arthritis.[81–83] However, MTX should be administered with caution in the case of diabetes and obesity, due to the increased risk of hepatic fibrosis when the cumulative dose exceeds 1.5 g.[84,85] Ciclosporin can increase insulin resistance, interfere with fatty acid metabolism favouring the development of dyslipidaemia and the increase of serum uric acid.[86] In a prospective cohort study on the Psocare registry, it was found that CsA was associated with a significant risk of developing diabetes at week 52, which is not surprising because the calcineurin inhibitors either tacrolimus and CsA are associated with a higher risk of

We **recommend** to be aware of signs and symptoms of anxiety and depression in patients with psoriasis and monitor 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[1] 100% agreement
We **suggest** using alternatives to brodalumab and apremilast in patients with a history of depression and/or suicidal ideation.	↑	EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 3 abstentions

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

A systematic review was conducted, see Methods & Evidence Report.

Results/Answer Although no treatment is fully contraindicated in case of diabetes, ciclosporin is better avoided because it could favour insulin resistance, particularly on long-term treatment course.

new-onset diabetes in transplant recipients.[87] The diabetogenic effect of CsA has been assumed to be related to inhibition of insulin secretion from pancreas islet cells,[88] 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.

Clinically significant dyslipidaemia has been rarely reported in patients receiving TNF-α antagonists, but this is not a

common issue in clinical practice.[89] A bodyweight gain could occur in patients treated with TNF-α antagonists.[90,91] In contrast, ustekinumab and IL-17 inhibitors usually do not increase bodyweight in patients with chronic plaque psoriasis.[92,93] Apremilast has been shown to cause weight loss in clinical trials.[93] Studies addressing the effects of TNF-α blockade on glucose homeostasis in patients with psoriasis and/or PsA were very limited and gave conflicting results. The Homeostasis Model Assessment (HOMA) and the Quantitative Insulin Sensitivity Check Index (QUICKI) are two widely used non-invasive surrogate markers of insulin resistance, used in the following studies. A study in 62 patients with chronic inflammatory rheumatic diseases, of whom 18 patients were affected by PsA, did not show any significant improvement in glucose homeostasis during the first six months of treatment with TNF-α inhibitors.[94] A recent prospective study in a cohort of 210 PsA patients treated with various anti-TNF-α inhibitors (adalimumab n = 70, etanercept n = 70) or MTX (n = 70) found that those receiving TNF-α inhibitors had significant improvements in glucose levels and other features of the metabolic syndrome compared with those treated with MTX.[95] Similarly, the effects of TNF-α inhibitors on insulin sensitivity/resistance in patients with psoriasis gave discordant results. A small randomized, double-blind study in twelve psoriatic patients at high risk of developing type 2 diabetes failed to observe a significant effect of a two-week treatment with etanercept on insulin secretion and sensitivity.[96] No significant changes in either insulin sensitivity or levels of fasting blood glucose were observed in a study in psoriatic patients after twelve weeks of treatment with adalimumab.[97] In contrast, in two different studies, respectively, on nine and 89 patients with plaque psoriasis etanercept improved insulin sensitivity.[98,99] Other TNF-α inhibitors also appear to improve insulin sensitivity in diabetic and non-diabetic patients with psoriasis.[100,101]

A pooled analysis of data from the phase III randomized controlled trials for secukinumab showed a neutral effect on fasting plasma glucose, lipid parameters and liver enzymes. In patients with fasting plasma glucose > 125 mg/dL at baseline (diagnostic criterion for diabetes) secukinumab treatment presented a trend towards lowering fasting glucose concentration compared to placebo treatment during the first 12 weeks.[102] Finally, patients with moderate-to-severe psoriasis are candidate for interventions aimed to reduce the cardiovascular risk. Screening for cardiovascular risks including diabetes, hypertension and dyslipidaemia should be recommended for all psoriasis patients.[18] Non-pharmacological interventions, such as bodyweight loss, should be recommended to obese patients. Indeed, it has been reported that low calorie diet inducing a moderate weight loss (i.e. 5 to 10% of bodyweight) increases the responsiveness of obese patients with moderate-to-severe chronic plaque psoriasis to systemic treatments.[103–106] Moreover, bodyweight loss could also increase insulin sensitivity in obese patients with psoriasis.

Psoriasis patients who suffered also from diabetes showed a lower response rate to secukinumab (n = 867) as well as to ustekinumab (n = 318) analysed in pooled phase III data from the FIXTURE, ERASURE and CLEAR study.[107] Pinter et al. suggested an up dosing to optimize the treatment outcome to 300 mg secukinumab every two weeks instead which is tested in patients >90 kg. The inflammatory history in cardiometabolic comorbidities including diabetes might rather influence the therapy response then the severity of psoriasis itself, which can be interpreted as an expression of the higher inflammatory burden.[107] However, further studies are needed to understand the mechanisms why cardiometabolic comorbidities are associated with lower response rates.

Etanercept does not have an impact on the glycaemic control in diabetes patients which was shown in the PRISTINE trial.[108]

Finally, it should be considered that diabetic nephropathy eventually occurring in patients with psoriasis could reduce the clearance of any systemic treatments for psoriasis including MTX and CsA.[109,110] CsA should be considered cautiously in patients with diabetes mellitus as significantly increased serum creatinine concentration could be observed.[111]

In addition to any medical treatment, appropriate supportive care should be offered, e.g. weight loss programmes for obese patients with metabolic syndrome or dyslipidaemia.

We **suggest against** using ciclosporin or MTX as a first line treatment in patients with diabetes and/or features of the metabolic syndrome.	↓	Consensus[1] 89% agreement EXPERT CONSENSUS
We **suggest against** using acitretin as a first line treatment in patients with dyslipidaemia.	↓	Strong consensus[1] 100% agreement EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 2 abstentions

3.6. Heart disease: How should psoriasis patients with ischaemic heart disease and/or congestive heart failure be managed?

This chapter is based on the related chapter in previous versions of this guideline.[7,8] A systematic search was conducted, details of which can be found in the Methods & Evidence Report.

Results/Recommendations

[a]Ischaemic heart disease/atherosclerosis

Summary/key points

- Patients with psoriasis have an approximately two- to three-fold increased relative risk to develop 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 guidance.[112]
- Patients without a history of cardiovascular disease should have their cardiovascular risk factors assessed and be given lifestyle advice including the avoidance of smoking, a healthy diet, increased physical activity and a healthy blood pressure with other treatment in accordance with current European Society of Cardiology guidance.[113,114]

We **suggest against** cyclosporine or acitretin as preferred treatments in patients with psoriasis and ischemic heart disease.	↓	Strong consensus[1]
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.	↑	100% agreement
We **suggest** anti-TNFs, ustekinumab, and IL-17 inhibitors as preferred targeted therapies in patients with psoriasis and ischemic heart disease*.	↑	EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 3 abstentions *In case of concormittant congestive heart failure, also note the reommendations from the respective section

- With the exception of methotrexate, there are no studies formally evaluating the effect of any antipsoriatic 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.
- 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 methotrexate, the anti-TNFs, in particular adalimumab, and ustekinumab 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. Moreover, inhibition of IL-17, especially with secukinumab, has shown to improve surrogate markers of endothelial dysfunction.
- 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 ischaemic heart disease or cardiovascular risk factors.
- There is no evidence that fumarates are associated with increased cardiovascular events in patients with ischaemic heart disease.
- Ciclosporine may induce or worsen arterial hypertension, a condition often found in patients with ischaemic heart disease, and worsen dyslipidaemia. The metabolism of ciclosporine may interfere with drugs used in patients with ischaemic heart disease such as beta-blockers or calcium antagonists.
- Acitretin has a very limited anti-inflammatory potential and may induce or worsen hyperlipidaemia.

Moderate-to-severe psoriasis is associated with several well-established cardiovascular risk factors including obesity, hypertension, diabetes, dyslipidaemia and metabolic syndrome.[115] Psoriasis severity has been linked to a higher prevalence of these risk factors. However, there is conflicting evidence as to whether psoriasis is associated with increased cardiovascular events and whether psoriasis itself represents is an independent cardiovascular risk factor.[116] Indeed, a large cohort study in Rotterdam found no difference in the risk of ischaemic heart disease hospitalizations in patients with psoriasis compared with matched control subjects.[117] Stern and Huibregtse[118] found that patients with very severe psoriasis have increased all-cause mortality, but that severe psoriasis is not an independent risk factor for ischaemic heart disease. The aforementioned studies are in contrast to a large and growing body of literature that suggests patients with more severe psoriasis carry a clinically relevant increased risk of mortality due to ischaemic heart disease. Samarasekera et al.[119]

critically evaluated 14 cohort studies and meta-analysed the magnitude of cardiovascular risk for the primary outcomes of cardiovascular mortality, stroke and myocardial infarction (MI). Increased risk was identified only in individuals with severe psoriasis (defined as requiring systemic therapy or hospital admission): the risk ratio relative to the general population was 1.37 (95% CI, 1.17–1.60) for cardiovascular mortality, 3.04 (95% CI 0.65–14.35) for MI and 1.59 (95% CI, 1.34–1.89) for stroke. The relative risks of cardiovascular disease were highest in the younger, severe psoriasis population (e.g. 3.10 [95% CI, 1.98–4.86] for MI at 30 years), and absolute risks were greatest in older individuals with severe psoriasis (e.g. 23.2 excess MIs per 10 000 person-years at 60 years).[119] Geata et al. showed an approximately 25% increased relative risk of cardiovascular disease in patients with psoriasis, independently of smoking, obesity and hyperlipidaemia.[120] The pooled relative risks for cardiovascular mortality in psoriasis compared with general population were 1.15 (95% CI 1.09–1.21) in all patients with psoriasis, 1.05 (95% CI 0.92–1.20) in those with mild psoriasis and 1.38 (95% CI 1.09–1.74) in severe disease.[39] A recent systematic review and meta-analysis indicate that subclinical coronary artery disease diagnosed with cardiac computed tomography angiography is more prevalent in patients with psoriasis, with an increased burden of disease and number of high-risk coronary plaques.[121]

It has been proposed that there may be overlapping immune pathways in both psoriasis and ischaemic heart diseases that may underlie this association[122,123] It is also a matter of great interest whether systemic antipsoriatic treatments affect cardiovascular risk by reducing the overall inflammatory burden. It is not known whether systemic treatments could modify cardiovascular outcomes including the rate of MI. However, studies investigating the effects of systemic treatments on cardiovascular risk factors including metabolic parameters (e.g. serum lipids), blood pressure or biomarkers of inflammation and atherosclerosis (e.g. C-reactive protein, endothelial dysfunction) have been completed. Multiple studies have failed to show any significant changes in metabolic parameters in patients receiving both PUVA and narrowband UVB therapy.[124,125] In contrast, systemic retinoids (i.e. acitretin) commonly increase serum triglycerides and cholesterol by shifting high-density lipoproteins to low-density lipoproteins.[125,126] Similarly, ciclosporin can increase serum lipids, plasma glucose and blood pressure in a dose-dependent fashion.[86,127] Therapy with MTX is associated with a reduced risk of cardiovascular morbidity and mortality in patients with RA as well as in patients with psoriasis and psoriatic arthritis.[128–131] In a longitudinal cohort study of 6902 patients with psoriasis, Ahlehoff et al. found that treatment with methotrexate was associated with reduced risk of cardiovascular events compared to patients treated with other antipsoriatic therapies such as ciclosporin and retinoids.[132] Methotrexate therapy decreases carotid intima–media thickness (a marker of arteriosclerosis) in patients with moderate-to-severe psoriasis.[133] Preclinical and pilot studies suggest possible cardioprotective effects of apremilast and fumarates but there is no clinical evidence that affect cardiovascular risk.[58,134]

The effect of biological therapies on the risk of ischaemic heart disease is unclear. Treatment with TNFi and ustekinumab has been shown to reduce aortic vascular inflammation and decrease systemic inflammatory biomarkers.[135–139] Moreover, therapy with TNFi improves biomarkers of atherosclerosis by reducing either intima–media thickness and arterial stiffness in patients with RA, spondyloarthropathies, PsA and psoriasis.[140–142] Secukinumab may have a beneficial effect on cardiovascular risk in patients with psoriasis by improving endothelial function measured by flow-mediated dilation.[143]

There is conflicting evidence on the effects of biologic therapy on the incidence of cardiovascular accidents in patients with psoriasis. A large cohort study of 25 554 patients with psoriasis followed for eight years using administrative and pharmacy claims data from a large U.S. insurer (i.e. United Health Group) did not show a reduced risk of MI in those receiving systemic therapy compared to those exposed to phototherapy.[144] A recent comparison of patients with first time hospital-diagnosed psoriasis between 1995 and 2002 (early era cohort) and those diagnosed between 2006 and 2013 (late era cohort) did not show any change in MI risk despite increased cardiovascular disease prevention and the availability of biologic therapy.[145] A meta-analysis of 22 randomized, placebo-controlled, double-blind studies of IL-12/23 antibodies and anti-TNF-α agents comprising 10 183 adult patients evaluated the possible association between biologic therapies and major adverse cardiovascular events (MACE). Compared with placebo, there was no significant difference in the rate of MACE observed in patients receiving anti-IL-12/IL-23 antibodies or anti-TNF-α treatments. However, the authors acknowledged that the study may have been underpowered to identify a significant difference.[146] However, other studies have shown different outcomes. In particular, Wu et al.[147] assessed whether patients with psoriasis treated with TNFi inhibitors had a decreased risk of MI compared with those treated with other systemic therapies, phototherapy or topical. This was a retrospective cohort study of 8845 patients, 1673 received a TNFi for at least two months, 2097 received conventional systemic treatments or phototherapy, and 5075 received only topical treatment. After adjusting for MI risk factors, the TNFi cohort had a significantly lower risk of MI compared with the topical cohort (adjusted hazard ratio, 0.50; 95% CI, 0.32–0.79). The difference in incidence of MI between TNFi and conventional systemic treatments or phototherapy was not significant.[147] In a Danish nationwide real-world study of 2400 patients with severe psoriasis enrolled in a registry, treatment with biological agents ($n = 693$) or MTX ($n = 799$) was associated with lower cardiovascular disease event rates than treatment with other antipsoriatic therapies.[148] This is consistent with Wu et al. who found that psoriasis patients receiving TNFis had a lower

major cardiovascular event risk compared to those receiving methotrexate and cumulative exposure to TNFis was associated with an 11% cardiovascular event risk reduction.[149] Concern was expressed over initial analyses linking IL-12/23 inhibitors with MACE in the first week of therapy. However, additional meta-analysis of clinical trials and data from registries in psoriasis and psoriatic arthritis suggest that licensed biologic therapies, including TNFi (adalimumab, etanercept and infliximab), anti-IL-17A agents (secukinumab and ixekizumab) or ustekinumab, are not associated with MACEs.[150–153] In a large prospective cohort study using the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), there were no significant differences in the risk of major cardiovascular events between etanercept, adalimumab, ustekinumab and methotrexate.[154] Similarly, in 60 028 patients with psoriasis or psoriatic arthritis from multiple US databases, no significant difference was found in the risk of MACEs after initiation of therapy with TNFi or ustekinumab.[155]

a. Heart failure

Summary/key points

- 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.[113]
- 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 ischaemic heart disease.
- Patients with suspected or confirmed heart failure should be referred to a cardiologist for investigation and treatment in accordance with current European Society of Cardiology guidance.[156]
- The 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
  - 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 and infliximab, worsen advanced heart failure and both drugs are contraindicated in patients with congestive heart failure NYHAIII/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 (CAVE 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 cyclosporine in patients with psoriasis and advanced congestive heart failure.	↓	Strong consensus[1] 100% agreement EXPERT CONSENSUS
We **suggest** that methotrexate, acitretin and apremilast are considered as treatment in patients with psoriasis and advanced congestive heart failure*.	↑	
We **suggest** that ustekinumab, inhibitors of IL-17 and of IL-23 are considered as treatment in patients with psoriasis and advanced congestive heart failure*.	↑	
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.	↑↑	

[1]Due to personal-financial conflict of interest 3 abstentions *In case of concormittant ischaemic heart failure, also note the recommendations from the resepective section

TNF-α in heart failure (HF) stems from the observations that TNF-α exerts negative inotropic effects and is capable of promoting fibrosis, hypertrophy and cardiomyopathy in animal models.[157] Moreover, cardiac-specific TNF-α levels are regulated by pressure and volume load in animals and in humans.[158] Therefore, a small series of clinical trials was conducted with TNFi to investigate its potential beneficial effects in patients with HF. Both RENAISSANCE and RECOVER[159,160] were large, multicentre, randomized, double-blind, placebo-controlled trials of

etanercept in HF. Both studies failed to show improved mortality or decreased hospitalizations due to CHF. The key finding of the RENAISSANCE trial was a trend towards higher mortality in etanercept-treated subjects, a concern heightened by the apparent dose–response relationship. The combined analysis of these studies showed a trend towards increased mortality and/or HF hospitalizations in the combined twice-weekly/thrice-weekly etanercept group compared with placebo.[159,160] Infliximab was evaluated in a phase II randomized, double-blind, placebo-controlled pilot study.[161] This pilot study did not show any beneficial effect of infliximab over placebo in terms of efficacy. Higher-dose infliximab (10 mg/kg) was associated with an increase in both all-cause mortality and the number of hospitalizations due to HF at weeks 28 and 54. In summary, the results of randomized, placebo-controlled trials with both etanercept and infliximab suggest a deleterious effect of higher doses of TNF blockers in patients with NYHA class III or IV HF. In particular, there was a trend towards higher mortality and a greater number of hospitalizations for HF. However, a recent Cochrane systematic review including 163 randomized controls trials with 50 010 participants and 46 extension studies with 11 954 participants found that the rate of new diagnosis of HF was not statistically significantly different between those patients treated with biologics and control treatments.[162] The cardiovascular safety data extracted from 74 articles, corresponding to 77 randomized controlled trials of TNFi, anti-IL-12/23, anti-IL-23 and anti-IL-17 agents for the treatment of psoriatic arthritis or psoriasis showed no significant difference in CHF incidence in patients receiving biological agents in comparison with placebo.[153] In conclusion, only moderate-to-severe CHF is a concern for initiating TNFi therapy in patients with psoriasis.

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

Narrative review of the existing literature was conducted.

Results/Answer A number of risk factors that predispose to chronic kidney disease (CKD) are especially prevalent in people with multiple comorbidity 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.[163] 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'.[164]

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 comorbidity

Systemic therapies *Acitretin.* National guidelines in the UK,[165] United States,[166] Spain[167] all recommend avoiding acitretin in moderate-to-severe renal disease, although no evidence is cited underpinning these recommendations. There were no studies identified that specifically address the use of acitretin for psoriasis in the context of CKD. Acitretin is widely used in the renal transplant population for skin cancer prophylaxis where stage 3 CKD is common; a recent systematic review in this population showed no increased in AEs when compared to placebo.[168] Limited data from RCTs do not indicate acitretin is a nephrotoxic drug. Acitretin is highly lipophilic, penetrates readily into body tissues and is highly protein (albumin) bound. Hypoalbuminaemia in association with CKD may therefore potentially increase drug clearance. It is metabolized in the liver to 13-cis acitretin and etretinate and then undergoes glucuronidation into inactive, water-soluble forms. In health, acitretin is excreted entirely in the form of these inactive metabolites, in approximately equal parts via the kidneys and the bile. In a single report,[169] the mean areas under the plasma concentration versus time curves of acitretin and 13-cis acitretin following a single oral dose of 50 mg of acitretin in six patients on haemodialysis were, in fact, about 50% lower than healthy controls. No retinoids were detectable in the dialysate.

In summary, acitretin is not known to be nephrotoxic and CKD (any stage) would not be predicted to markedly impact on drug disposition.

Apremilast. Apremilast has no known nephrotoxic potential. In the pivotal clinical trials, there was no evidence for treatment emergent adverse events related to renal function.[74,170]

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. When starting treatment with apremilast in case of severe renal insufficiency, only the morning dose should be given as total daily dose (recommendations according to SmPC).

Fumarates. Fumarates are known to be potentially nephrotoxic and may rarely cause an irreversible, proximal renal tubular nephropathy with long-term use. Recent studies[171] 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 health, fumarates are extensively metabolized by ubiquitous esterases,

and so CKD would not be predicted to significantly impact on drug clearance.[172,173]

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[174,175] 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). In one long-term psoriasis study, patients with a pretreatment creatinine of >100 μmol/L were more likely to discontinue therapy. In a study performed in patients with (stage 5) terminal renal failure, the systemic clearance was approximately two thirds of that in patients with normally functioning kidneys. Less than 1% of the administered dose is removed by dialysis.

Guidelines recommend using CsA with caution in people with CKD; in those with significant reduction in renal function (CKD stage 3 or more,[176] CsA nephrotoxicity may lead to further critical reduction in function.

Methotrexate. MTX is not generally considered nephrotoxic when used at low doses for inflammatory disease, although renal impairment is reported[177] and may be an under-recognized event. MTX 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. In a cohort of 77 patients with RA and various stages of CKD, the elimination half-life of a single dose of intramuscular MTX (7.5–15 mg) was directly related to GFR, with a decrease in MTX of 44.7% in the category of patients with the poorest renal function (i.e. creatinine clearance <45 mL/min, roughly equivalent to stage 3b).[178] Pooling data from RCTs of MTX for RA also indicate that presence of renal impairment (creatinine clearance <79 mL/min) increases the OR for severe and pulmonary toxicity by four compared to those with a creatinine clearance >99.8 mL/min (reference group).[179] There are no studies evaluating use of MTX for psoriasis with CKD. US guidelines[166] consider renal impairment a relative contraindication to MTX, and all recent RCTs with a MTX arm exclude patients with 'significant' renal impairment. There are several case reports of life-threatening toxicity following MTX use in people on dialysis (reviewed in Ref. [180]). Guidelines in the rheumatology literature, largely consequent on the two studies referenced above, recommend avoiding MTX in people with creatinine clearance of <20 mL/min and to halve the dose in those between 20 and 50 mL/min (summarized in Ref. [181]).

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

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

We **recommend** ensuring an accurate assessment of renal function in any psoriasis patient with known or suspected chronic kidney disease prior to therapy.	↑↑
We **recommend** working in collaboration with the nephrologist when prescribing systemic therapy 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/1.73m²). **(carefull dosing/dose adjustment may be needed)*	↑
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/1.73m²).	↓↓

Strong consensus[1]

100% agreement

EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 3 abstentions

Narrative review of the existing literature was conducted.

Results/Answer *Standard systemic therapy. Ciclosporin*—Neurotoxicity is a well-established complication of CsA although receives surprisingly little attention in literature. A comprehensive review[182] referencing data from (primarily) the transplant population estimated that 10% and 28% of patients receiving calcineurin inhibitors experience neurotoxic side-effects ranging from mild paraesthesia and peripheral neuropathy through to centrally mediated complications such as altered cognition, visual disturbances and seizures. Of these tremor and paraesthesia are the most common, and in the early trials in psoriasis, affected 40% and 25% of participants receiving 5 mg/kg,

respectively.[183] Calcineurin is major component of neural tissue and plays a key role in the regulation of nerve cell function and neurotransmission[184,185]; toxicity is dose-dependent and largely reversible. Ciclosporin does not readily cross the blood–brain barrier, so conditions that disrupt the integrity of this, such as neurodegenerative disease, systemic infections or hypertension, may perhaps also make patients more prone to the neurotoxic effects of CsA.[184] Additional factors such as CsA-related hypomagnesaemia[186] may also contribute. No studies were identified specifically reporting on outcomes in people with pre-existing neurological disease treated with CsA for psoriasis. Existing guidelines and the SmPC do not stipulate neurological disease to be a contraindication to treatment.

Fumarates—Dimethyl fumarate (DMF) has more recently been licensed and developed for use in psoriasis and is also a licensed treatment for MS (reviewed in Ref. [187]) at doses of 240 mg BID. Fumarates may be a preferred option for the treatment of psoriasis in people with established MS. There have been a total of nine reports of confirmed progressive multifocal leukoencephalopathy (PML) in patients with psoriasis treated with fumarates; six with Fumaderm®, two with Psorinovo® (a slow-release DMF formulation) and one with compounded fumaric acid esters.[188–196] In all cases, a degree of lymphopenia and/or other contributary factors for PML is thought to have been of direct aetiological relevance.

Methotrexate—CNS toxicity is a well-recognized AE of high dose MTX, especially with intra-thecal administration. Low-dose oral and s/c MTX have rarely been reported to cause a reversible leukoencephalopathy (see Ref. [197,198] for recent reports and reviews). The SmPC cites drowsiness, ataxia, blurred vision, transient subtle cognitive dysfunction, mood alteration and unusual cranial sensations as occasionally reported with low-dose MTX. No studies were identified specifically reporting on outcomes in people with pre-existing neurological disease treated with MTX for psoriasis. Existing guidelines and the SmPC do not stipulate neurological disease to be a contraindication to treatment.

Biological therapy *TNF antagonists.* In vitro, murine and human data suggest that TNF has an important role in the pathogenesis of inflammatory demyelinating disease (reviewed in Ref. [199]). However, an early report of increased lesion activity in two MS patients receiving infliximab[200] as well as the withdrawal of lenercept (a soluble p55 receptor developed for the treatment of MS) due to increasing severity and duration of symptoms in clinical trial subjects led to heightened awareness of potential risk of TNF antagonist therapy in the context of MS. More recently,[201] the single nucleotide polymorphism (SNP) rs1800693 in the TNFRSF1A gene associated with MS but not psoriasis (or other autoimmune conditions) has been shown to direct expression of a novel, soluble form of TNFR1 that can block TNF, hence lending further biological plausibility to a causal relationship between TNF antagonism and demyelination.

wAll five TNF antagonists have been associated with aggravation of MS and/or new-onset central demyelination which have been reviewed by Mahil *et al* and Bosch *et al*.[202,203] Case reports in more recently licensed anti-TNF agents golimumab[204,205] and certolizumab[206] have been described. Of 84 cases of central demyelination reported in patients with psoriasis, the majority occurred within the first year of therapy; 33% (25/76) achieved complete recovery after cessation of anti-TNF +/− adjunctive therapy, 72% (55/76) did not achieve complete clinical recovery after cessation of TNF antagonist therapy. There were fourteen cases of worsening neurological disease despite cessation of anti-TNF therapy and several reports of new, clinically silent lesions detected on follow-up imaging.[202,205–216]

A case–control study in rheumatoid arthritis using a Canadian administrative claims and electronic medical records database showed a trend towards an increased rate of demyelination in 891 patients with no risk factors (for demyelination) with the authors suggesting that TNF antagonist therapy may increase risk of truly incident demyelinating events by ~30%, although failed to meet statistical significance (adjusted rate ratio 1.31 [95% CI 0.68–2.50]).[217] To date, trial and pharmacovigilance registry data have not shown any increased risk although this may relate to a low overall incidence, as well as exclusion of people at particular risk.

With respect to peripheral disease, all forms of demyelinating neuropathies, including Guillan–Barre syndrome, Miller–Fisher syndrome, multifocal motor neuropathy with conduction blocks, Lewis–Sumner syndrome and chronic polyradiculoneuritis have been reported in association with TNF antagonist therapy, although numbers of case reports in the literature are fewer when compared to central demyelination.[203,218,219] One report of five patients providing longer-term data (up 3–4 years) indicated that once triggered, chronic demyelinating neuropathy may persist or recur irrespective of whether the TNF antagonist is discontinued.[219] Isolated cases of axonal neuropathy and vasculitic neuropathy are also reported.[203] US, UK and German psoriasis guidelines all advise avoidance or caution with TNF antagonists in people with demyelination and caution in those at risk.

IL-12/23 pathway inhibitors. The IL (interleukin)-12 p40 family of cytokines (IL-12 and IL-23) has been strongly implicated in the pathogenesis of both MS and experimental autoimmune encephalomyelitis (EAE), an animal model that mimics many clinical and histological characteristics of MS. This prompted a phase II study evaluating the role of ustekinumab in patients with relapsing and remitting MS. Patients were randomly assigned 1:1:1:1:1 to placebo or 27 mg, 90 mg

or 180 mg ustekinumab every four weeks or 90 mg ustekinumab every eight weeks up to week 23. A total of 200 patients received at least one dose of ustekinumab and while there was no evidence of benefit, there was no evidence of worsening neurological disease or increase in AEs when compared to placebo. To date, there has been one case report of primary progressive MS in a patient taking ustekinumab for refractory Crohn's disease[220] with the first neurological symptoms occurring around one year into therapy. She had received TNF antagonist therapy (infliximab, adalimumab and certolizumab) prior to ustekinumab. With respect to peripheral demyelinating disease, a single case of Guillain–Barré has been reported in a 23-year-old man with refractory Crohn's disease one year after commencing treatment with ustekinumab, having previously been treated with adalimumab.[221] A further isolated case of peripheral neuropathy of unspecified aetiology after three doses of ustekinumab was reported in an observational, retrospective 5-year follow-up study of ustekinumab in psoriasis.[222] Furthermore, the first case of reversible posterior leukoencephalopathy syndrome (RPLS) in a 65-year-old woman who received ustekinumab for over 2.5 years for psoriasis has been reported. She presented with mild hypertension, confusion, headache, nausea, vomiting, multiple seizures and computed tomographic scans and magnetic resonance images of her head revealed characteristic findings of RPLS. Complete clinical recovery and reversal of the radiologic findings occurred, which is also considered typical of RPLS.[223] No data on the newer p19 inhibitors were identified.

Il-17 inhibitors. The IL-17A/F pathway is implicated in both psoriasis and multiple sclerosis, with elevated levels of IL-17A and IL-17F levels detected in both diseases.[224] Phase II randomized controlled data have shown encouraging results with secukinumab associated with a reduction in both the number of active and new MRI brain lesions in patients relapsing–remitting MS which were reduced by 49% and 67%, respectively[225]; but this is yet to be replicated in further studies. There are five cases in the literature of patients receiving secukinumab for immune-mediated inflammatory diseases with concomitant MS. 80% (4/5) of patients with MS remained stable with no progression of disease and achieved remission of psoriasis/psoriatic arthritis/ankylosing spondylitis. 20% (1/5) had a relapse of MS and required treatment with rituximab.[226–229] There are no reported de novo cases of central demyelination with secukinumab; however, longer-term safety data are required. No data on other IL-17 agents (ixekizumab, brodalumab) were identified.

Summary and synthesis 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 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 MS[230] and that asymptomatic first-degree relatives may have morphological evidence of subclinical disease and/or CSF oligoclonal bands (reviewed in Ref. [231]), 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 leucocyte counts is strongly recommended in order to minimize the risk of PML. Ustekinumab p19 and anti–IL-17 represent alternative treatment options.

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

We **suggest** using fumarates in psoriasis patients with multiple sclerosis.	↑	Strong consensus[1]
We **recommend against** using TNF antagonist therapy in psoriasis patients with a diagnosis of multiple sclerosis or other demyelinating disease.	↓↓	100% agreement
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.	↓	EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 3 abstentions

A systematic review was conducted, see Methods & Evidence Report.

Results/Answer

The available data published are insufficient to give strong recommendations for or against using the available antipsoriatic drugs in patients with moderate-to-severe psoriasis and concomitant hepatitis B. Table 4 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

Screening

We **recommend against** screening for **hepatitis A** as a routine measure before starting a systemic treatment.	↓↓	Strong consensus[1] 100% agreement EXPERT CONSENSUS
We **recommend** screening patients for **hepatitis B** (HBsAg, anti-HBsAg, anti-HBcAg) as a routine measure before starting a treatment with cyclosporine, methotrexate or biologics.	↑↑	Strong consensus[1] 100% agreement EXPERT CONSENSUS
We **recommend** to follow the algorithm presented in fig. 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[1] 100% agreement EXPERT CONSENSUS
In case of positive findings for **hepatitis C**, we **recommend** referral to a hepatologist.	↑↑	

[1]Due to personal-financial conflict of interest 2 abstentions

Choice of treatment

We **recommend** that treatment decision for patients with positive test result for HBsAg or positive HBV DNA should always be taken together with a hepatologist.	↑↑	Strong consensus[1] 100% agreement EXPERT CONSENSUS
Depending on the individual health care setting and personal experience and training, we **suggest** to consult 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[1] 100% agreement EVIDENCE AND CONSENSUS BASED, see METHODS & EVIDENCE REPORT
We **recommend** regular testing for HBsAG/HBV-DNA (e.g. every three months) during systemic treatment.	↑↑	Strong consensus[1] 100% agreement EXPERT CONSENSUS
We **recommend** to record all treatment initiations and follow up visits of psoriasis patients with concomitant hepatitis B or C cases in drug registries.	↑↑	Strong consensus[1] 100% agreement EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 2 abstentions

exposed to the drug. For detailed information, see methods report.

[1]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 methods 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 holds particularly true for methotrexate, where study data indicate at least no increase in liver fibrosis.[232]

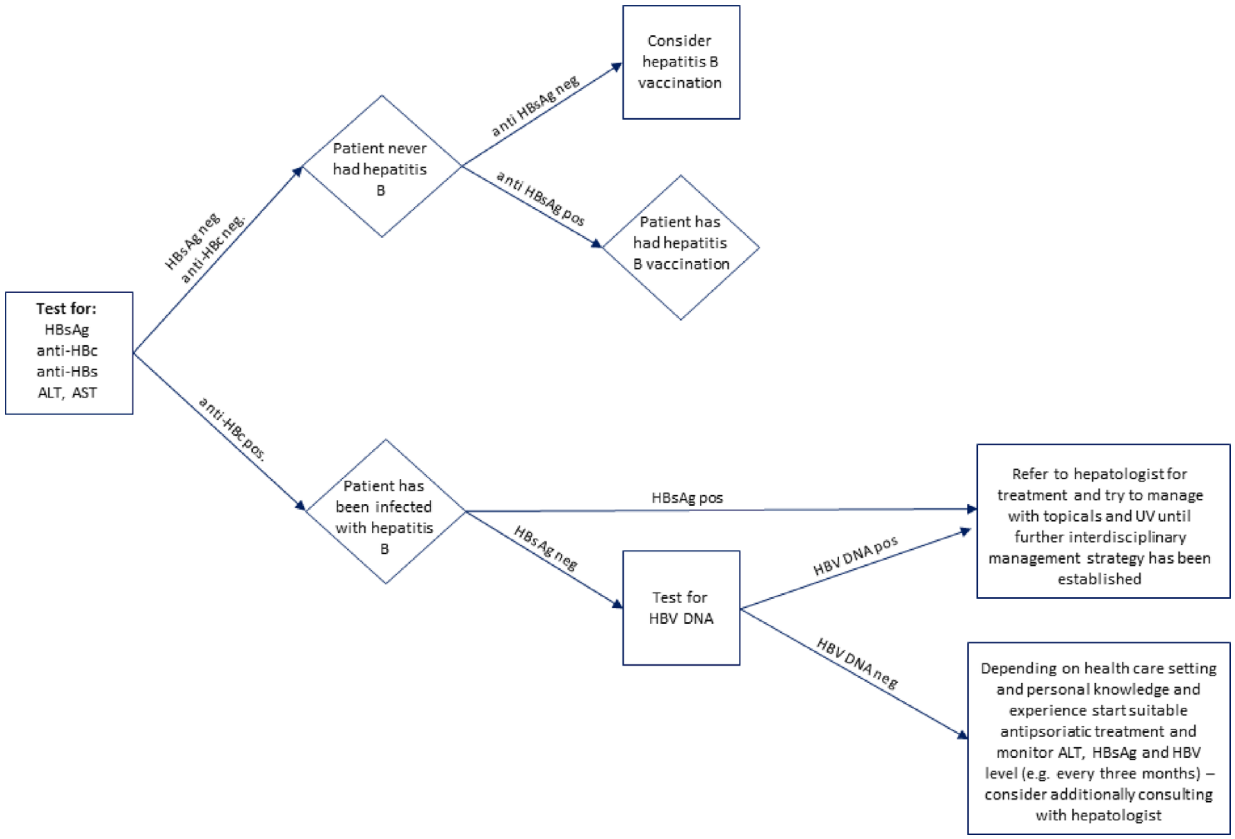

Figure 1 Algorithm for the interpretation of the hepatitis B test results.

Table 4 Risk of hepatitis B reactivation during psoriasis treatment

Systemic treatments		Case of hepatitis B reactivation during psoriasis treatment identified in systematic search
Conventional systemic agents	Acitretin	No
	Ciclosporin	No
	Fumarates	No
	Methotrexate	No
Small molecules	Apremilast	No*
Anti-TNF alpha	Etanercept	Yes (see methods report for details)
	Infliximab	Yes (see methods report for details)
	Adalimumab	Yes (see methods report for details)
	Certolizumab	?
Anti-IL 12/23	Ustekinumab	Yes (see methods report for details)
Anti-IL 17	Secukinumab	Yes (see methods report for details)
	Ixekizumab	No*
	Brodalumab	No*
Anti-IL 23	Guselkumab	No*
	Tildrakizumab	No*
	Risankizumab	No*

[1]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 methods report.

Tuberculosis screening
Diagnostic for TB, regardless Bacillus Calmette-Guérin (BCG) vaccination, prior to and during follow up with biologic. One must be alert for TB infections during biologic treatment to six months after discontinuation. During treatment, rescreening for LTBI is recommended and frequency should be based on: anamnesis, risk of exposure, as well as tuberculin skin test (TST) and interferon gamma release assay (IGRA) results.
1. Anamnesis: • Symptoms suspicious for TB • History of TB, adequate treatment • Exposure to TB • Origin from or recently stayed for a long time in an endemic area • High risk patient • BCG vaccination
2. Physical examination, to consider: • Auscultation of the lungs if symptomatic (not-specific for TB diagnosis) • Scar (left) upper arm (may indicate a BCG vaccination) • Enlarged lymph nodes, abscess scars
3. Chest X-ray: (If the chest X-ray has been performed more than 3 months ago, a new chest X-ray is required.) • Suspicious for active, LTBI or history of TB? → Consult pulmonologist if abnormalities
4. TST* and/or IGRA • If IGRA and TST are performed, the IGRA can best be drawn right after the TST is assessed. If drawing is done more than three days after the TST, the TST can booster the IGRA and result in a false-positive response. • The recommendation to perform IGRA testing rather than TST testing is strong for those who have received the BCG vaccination.

*It is necessary to follow the local recommendations, as the threshold for the TST is different among countries and even among regions within the same country. In most of the countries ≥ 5 mm is considered positive

TST*	IGRA	Diagnosis	Policy
<5 mm	negative	Depends on anamnesis	• If no TB suspicious anamnesis or symptoms, no history of TB, no TB exposure, not from or recently from an endemic area, and no high risk patient, a biologic can be applied. • If yes: Consult pulmonologist for any further diagnosis and treatment • TB infection can still be present in HIV-infected patients with a low CD-4 count
≥5 mm <10 mm	negative	LTBI or active TB with false negative IGRA, or false positive TST	Consult pulmonologist for any further diagnosis and treatment
>10 mm	negative	Strongly consider LTBI or active TB with false negative IGRA, or false positive TST	Consult pulmonologist for treatment
Every result	QFT-G 0.2-0.35 U/ml	Consider LTBI or active TB, or IGRA false positive	Consult pulmonologist for any further diagnosis and treatment
Every result	Positive (QFT-G > 0.35 U/ml)	Strongly consider LTBI or active TB	Consult pulmonologist for treatment

*It is necessary to follow the local recommendations, as the threshold for the TST is different among countries and even among regions within the same country. In most of the countries ≥ 5 mm is considered positive

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

This chapter is based on the related chapter in previous versions of this guideline.[7,8] A systematic search was conducted, details of which can be found in the Methods & Evidence Report.

Results/Answer Current guidelines and recommendations for screening for tuberculosis (TB) vary between countries and specialities. There are variations in the recommended diagnostic tests, cut-off values, follow-up and preventive therapy regimens. A uniform approach for the diagnostic procedures and the interpretation of the test results for latent tuberculosis infection (LTBI) screening may reduce the cases of reactivation, but giving binding pan-European recommendations is partly hampered by different regional regulations. For recommendation for which treatment TB screening is recommended, please see respective drug chapters.

Tuberculin skin test (TST) False-negative TST includes those related to the protein purified derivative (PPD) (PPD expiration, experience or loss of antigen [e.g. subcutaneous administration]), and those related to the situation of the patient (HIV infection, recent infections and vaccinations, malignancy, metabolic diseases, immunosuppressant therapy or extreme ages [newborn, elderly]). False-positive TST includes those related to the administration and PPD lecture (inexperience, high amount of antigen) and cross-reactions (BCG vaccination and most environmental

We **recommend** to do tuberculosis screening according to local regulations.	↑↑	Strong consensus[1]
For pre-screening, we **recommend** anamnesis including tuberculosis history; a chest X-ray; TST and/or IGRA.	↑↑	100% agreement
We **recommend** remaining alert to the possibility of tuberculosis infection during therapy. This includes taking medical history and might include tuberculosis testing.	↑↑	EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 4 abstentions

We **recommend** to discuss the decision to initiate immuno-suppressive therapies in patients with signs for latent tuberculosis case-by-case with an infectious disease specialist.	↑↑	Strong consensus[1]
As a commonly used procedure in case of latent TB, a treatment with isoniazid can be **recommended** with treatment initiation one month before the start of the immunosuppressive therapy and should be continued for 6 months (for alternatives see Table 5).	↑↑	100% agreement EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 4 abstentions

non-tuberculous mycobacteria). Although a BCG vaccination or an atypical mycobacterial infection may cross-react with the TST, causing a false-positive result, the tuberculin reaction would usually be much higher if active TB is truly present. The BCG vaccination may fade over time and no cross-reaction would occur. Regardless the BCG vaccination, in general, an assessment of ≥5 mm induration will be considered as positive. A patient may then be referred directly to the pulmonologist. In patients with a history of BCG vaccination, IGRA testing is preferred over TST.

IGRA IGRA is a specific blood test. After a *Mycobacterium Tuberculosis* infection, T cells will release interferon-gamma (IFN-γ) in response to contact with the TB antigens. Two measurements for interferon-gamma are known; the QuantiFERON®-TB Gold test (QFT-G), based on the amount of IFN-γ that is released in response to the antigens, and the T-SPOT® TB test (T-SPOT), counting the number of T cells that produce IFN-γ in a sample of blood. The IGRA is not affected by prior BCG vaccination; however, the interpretation of results (borderline results) might be limited due to issues in the cut-off values, shifting conversions and reversion rates over time, and varying test reproducibility. Neither TST or IGRA allows to distinguish between active or latent TB.[233] A suppressed immune system 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. A negative IGRA, following a positive TST, can still suggest a LTBI. Besides, the IGRA can be unreliable (false negative) if other immunosuppressive medication was applied in advance. An IGRA is also recommended if the TST was less than 5 mm induration. Negative results of TST or IGRA of HIV-infected patients with a low CD-4 count cannot rule out a TB infection.

Screening during biologic treatment Physicians have to be aware that there is still a risk of active tuberculosis under biologic therapy, even if LTBI was correctly treated. Therefore, rescreening on LTBI is preferable during biologic treatment. The frequency should take risk exposure into consideration. Besides medical history, both TST and IGRA are recommended, because of the influence that the biologic may have (false-negative) on these tests. A high index of suspicion should also be maintained for 6 months following discontinuation.

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

This chapter is based on the related chapter in previous versions of this guideline.[7,8] A systematic search was conducted, the details of which can be found in the Methods & Evidence Report.

Results/Answer Comment: Depending on the prevalence of TB and on the healthcare situation, dermatologists may be in a position to interpret positive findings and to make further

Table 5 Therapeutic regimens for LTBI

Drug	Dose	Treatment duration
INH alone (daily)	5 mg/kg; max dose: 300 mg	6–9 months
RIF alone (daily)	10 mg/kg; max dose: 600 mg	3–4 months
INH + RIF (daily)	INH: 5 mg/kg; max dose: 300 mg RIF: 10 mg/kg; max dose: 600 mg	3–4 months

INH, isoniazid; RIF, rifampicin, treatments with pyrazinamide should be avoided (high risk of hepatotoxicity). Based on WHO: Latent tuberculosis infection: updated and consolidated guidelines for programmatic management, 2018.

Table 6 LTBI screening indication based on different systemic treatments

Systemic treatments		SmPC	Comments
Conventional systemic agents	Acitretin	No	No cases of reactivation have been reported[246]
	Ciclosporin	No	Cases have been reported in organ transplant patients with high doses of CsA[246]
	Fumarates	No	No cases of reactivation have been reported[247,248]
	Methotrexate	√	Cases of reactivation have been reported[249]
Small molecules	Apremilast	No	Increased risk has not been reported[250]
Anti-TNF alpha	Etanercept	√	Increased risk of reactivation has been reported[251,252]
	Infliximab	√	Increased risk of reactivation has been reported[251,252]
	Adalimumab	√	Increased risk of reactivation has been reported[251,252]
	Certolizumab	√	Increased risk of reactivation has been reported[246,251]
Anti-IL-12/23	Ustekinumab	√	Uncertain risk of reactivation (cases have been reported)[246,253]
Anti-IL-17	Secukinumab	√	Increased risk has not been reported in clinical trials[253]
	Ixekizumab	√	Increased risk has not been reported in clinical trials[253]
	Brodalumab	√	Increased risk has not been reported in clinical trials[253]
Anti-IL-23	Guselkumab	√	Increased risk has not been reported in clinical trials[254]
	Tildrakizumab	√	Increased risk has not been reported in clinical trials[255]
	Risankizumab	√	Increased risk has not been reported in clinical trials[256]

Reported cases need to be seen in correlation to approval date, especially with years and numbers of psoriasis patients exposed to the drug.

management decisions themselves or direct referral to infectious disease specialists with interdisciplinary cooperation may be common.

Interpretation of positive findings in IGRA/TST. Patients with active and latent tuberculosis (TB) can be identified using either the interferon-gamma release assay (IGRA) or tuberculin skin test (TST). However, neither test can distinguish between the latent and active states of the disease.[233]

IGRA 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.[233]

The sensitivity of **TST** for latent tuberculosis infection (LTBI) has been described as 74% and the specificity of 89% in a meta-analysis.[234,235] The positive predictive value for TB infection by the TST depends on the prevalence of TB within a given region/population and the possibility of cross-reactions.

False-positive TST includes those related to the administration of purified protein derivative (PPD) and its lecture (inexperience, high amount of antigen) and cross-reactions (BCG vaccination and most environmental non-tuberculous mycobacteria). Although the TST would usually be, much higher if active TB is truly present.

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[236] and urinalysis (pyuria).[237–239] For details of differential diagnosis of latent versus active TB, please see respective guidelines and reviews.[233,236,240]

Different treatment regimens are available for LTBI with duration depending on monotherapy or combinations. In clinical practice, the most widely accepted treatment is isoniazid (INH) six months and INH + rifampicin (RIF) three months, see Table 5.[241] Patients during chemoprophylaxis treatment should be checked regularly to detect any drug-related adverse events (e.g. hepatotoxicity) and need monitoring for symptoms of TB during treatment with biologics since reactivation has been reported even after screening and chemoprophylaxis for LTBI has been completed.[43]

Risk of TBC reactivation with different treatments *Conventional treatments/Small molecules.* Data on reactivation risk with acitretin, ciclosporin (CsA), fumarates and methotrexate (MTX) and apremilast are scarce. Most published guidelines so far have not recommended TB screening for these drugs (except MTX and CsA).[242] Screening before treatment for MTX is

We **recommend against** TNF alpha antagonists as a treatment for patients with latent TB unless there are no other suitable treatment options.	↓↓	Strong consensus[1]
We **recommend** remaining alert to signs and symptoms of tuberculosis activation or re-infection during therapy.	↑↑	100% agreement
We **suggest** acitretin, apremilast or fumarates or a treatment from the anti-IL 17 and anti-IL 23 group for patients with latent TB that require a systemic antisporiatic treatment.	↑	EXPERT CONSENSUS

[1]Due to personal-financial conflict of interest 4 abstentions

recommended in the summary of products characteristics (SmPC). The sensitivity of IGRA and 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.[243]

Biologics. A higher risk of latent TB reactivation with infliximab and adalimumab, followed by etanercept has been identified. Cases of latent TB reactivation with ustekinumab have been reported in a long-term study of up to 5 years.[151] The risk of latent TB reactivation seems to be lowest during treatment with anti-IL-17 and anti-IL-23 targeted treatments.[43,244]

In a systematic review by Snast et al., 78 patients who developed active TB during biologic treatment were analysed. Eighty per cent 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 and active TB and presented mostly with extra-pulmonary disease within the first six months of biologic therapy.[245]

Table 6 provides an overview of the screening practice based on reactivation risk during 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 favour the group of anti-IL-17 and anti-IL-23 as treatment options. IL-12 has been reported to play a role in the anti-TB immune response.

3.12. 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.[7,8] A systematic search was conducted, details of which can be found in the Methods & Evidence Report.

Results/Answer 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.[257,258] Conversely in the postpartum 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,[259] 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.[260,261] The risk of untreated psoriasis of the mother in pregnancy must therefore be weighed against any potential harm through drug exposure of the fetus. Other factors that may impact pregnancy outcomes include alcohol consumption, smoking and comorbidities such as obesity and depression (which are more prevalent in greater disease severity).[262] Despite the rapidly increasing number of medications available for the treatment of psoriasis, knowledge on their safety in pregnancy remains limited.

Non-biologic systemic drugs *Acitretin.* Acitretin is teratogenic and is contraindicated in women of childbearing potential, those planning pregnancy, breastfeeding or not capable of using contraception until 3 years after cessation of therapy.[263]

Apremilast. There are limited data about the use of the small molecule inhibitor apremilast during pregnancy. Previous studies on animals did not show an increase in malformations with apremilast, but have shown dose-related fetal loss and reduced birth weight. Apremilast is therefore contraindicated during pregnancy.[264] Women of child-bearing potential should use effective contraception to prevent pregnancy and continue this until at least four weeks after cessation of apremilast treatment.[264]

Apremilast was detected in the milk of lactating mice at levels approximately 1.5-fold that of blood plasma samples.[265,266] It is unknown whether apremilast or its metabolites are excreted in breastmilk in humans; therefore, apremilast should not be used while breastfeeding.[264,266] No data are available regarding the influence of apremilast on fertility in humans.[264]

Ciclosporin. Ciclosporin crosses the placenta, but there is no evidence for teratogenicity.[267] Experience with solid organ transplant recipients indicates that ciclosporin increases the chance of pregnancy-specific complications such as pre-eclampsia and low birthweight. In pregnant women with plaque psoriasis receiving ciclosporin, the advantages and disadvantages of continuing ciclosporin should be considered. Ciclosporin should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.[267] The ethanol content of the Sandimmun Neoral formulations should also be taken into account in pregnant women.

If necessary, ciclosporin treatment can be continued with close follow-up, preferably together with an obstetrician.[267,268]

Ciclosporin is transferred into breastmilk; therefore, ciclosporin use is contraindicated during breastfeeding. There are limited data on the effect of ciclosporin on human fertility.

Dimethyl fumarate—Dimethyl fumarate is contraindicated in women of child-bearing potential who are not using appropriate contraception.[269] Dimethyl fumarate should not be taken by women who are pregnant, breastfeeding or attempting conception. There are no published reports of patients becoming pregnant while on dimethyl fumarate.[270] No data are available on the effects of dimethyl fumarate on female fertility.[269] In patients with diarrhoea during treatment with dimethyl fumarate, the effect of oral contraceptives can be reduced. Additional use of barrier methods of contraception is therefore recommended.[269]

It is unknown whether fumaric acid esters or metabolites are excreted in breastmilk; therefore, use of dimethyl fumarate is contraindicated during breastfeeding.[269]

Methotrexate—Methotrexate is a folic acid antagonist known to be teratogenic in humans. In a recent review, statistically significantly higher proportions of microcephaly, craniosynostosis, tetralogy of Fallot, pulmonary valve atresia, limb reduction defects and syndactyly were found in newborns after maternal use of methotrexate in pregnancy.[271] Spontaneous abortions were observed more frequently in pregnant women receiving methotrexate (less than 30 mg/week) compared to women with comparable diseases treated with other medications (42.5% vs. 22.5%).[272]

Therefore, where relevant, women should be counselled about pregnancy and breastfeeding and should not conceive while taking methotrexate.[272] Recent EMA guidelines recommend discontinuing methotrexate for 6 months before attempting conception, which is a change from the previous recommendations of 3 months.[273] No evidence pertaining to the standard dose of methotrexate (5–30 mg/week) for inflammatory diseases is cited for this change of recommendation. The practice of the guideline group differs from this in favour of a shorter period of discontinuation (3 months).

It is recommended that sexually active women have a pregnancy test prior to starting therapy and use two methods of contraception throughout the period of methotrexate treatment. In the event of pregnancy during methotrexate therapy, immediate referral to an obstetrician is required.[274] Methotrexate influences oogenesis and possibly can reduce fertility, especially in high doses. In most patients, this is reversible after stopping methotrexate.[272] Methotrexate is excreted into breastmilk and so should not be used when breastfeeding.

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.

Biologic drugs Data from studies reporting pregnancy outcomes in women exposed to biologic treatments during conception and/or pregnancy were recently comprehensively reviewed as part of the British Association of Dermatologists guidelines for biologics use in psoriasis.[275] 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.[276,277] 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 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.[278] 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.[279] 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.[280] Infliximab and adalimumab could be detected in the infants for as long as 6 months. Postmarketing prospective pharmacokinetic research has confirmed no/minimal transfer of certolizumab pegol via the placenta (CRIB study, $n = 16$[281]) and into breastmilk (CRADLE study, $n = 19$[282]).

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[283–295] (see respective table). 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, preterm births or neonatal infections.[283–295] One study (in inflammatory bowel disease) addressed maternal infection, indicating a potential increased risk to the mother following TNF antagonist exposure.[287]

The evidence is overall limited since most studies involved small cohorts that may be underpowered to demonstrate small but significant risks associated with the treatments. Most of the evidence also relates to women with other chronic

We **suggest** ciclosporin as a first line convention agent in women planning conception and when it is necessary to start systemic therapy during the 2nd and 3rd trimester of pregnancy	↑	
Methotrexate and acitretin are contra-indicated in women planning conception. We **recommend against** using these.	↓↓	Strong consensus[1]
Fumarates and apremilast are contra-indicated in women planning conception. We **suggest against** using these.	↓	100% agreement
We **recommend** consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems	↑↑	EXPERT CONSENSUS
We **recommend** the collection of maternal exposure to medications and pregnancy outcome data in national safety registries where available.	↑↑	

[1]Due to personal-financial conflict of interest 3 abstentions

inflammatory conditions such as inflammatory bowel disease or arthritis rather than psoriasis specifically. Several of the outcomes were poorly defined and heterogeneous, making it difficult to ascertain whether or not a pattern of specific birth defects was occurring. There is also a paucity of information on long-term outcomes for children born to women receiving biologics.

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.

Necessity for continuing contraception immediately following biologic treatment cessation There is no general consensus on how long contraception needs to be continued after stopping treatment with a biologic. Table 7 gives an overview of the recommended minimum time lag between stopping a biologic treatment and conception, as stated in the respective SmPCs. For treatments with a good safety profile during pregnancy, continuation of contraception immediately following treatment cessation may not be as relevant as for treatments with an unknown or less favourable safety profile. It is worth noting, that active placental transfer of biologics starts to occur around 13 weeks' gestation and increases significantly after 20 weeks' gestation. The specific half-lives of the respective drugs impact the remaining drug level at these time points.

Paternal use In men who are planning conception, the effects of systemic medications on both fertility and fetal development are important considerations. However, there are very limited data on the impact of paternal exposure to systemic medications, particularly with respect to teratogenicity and longer-term sequelae.

Acitretin. Acitretin has no known effect on male fertility.[296] Traces of acitretin have been reported in the semen of men; however, there is no evidence of teratogenicity at conception as the main at-risk period is 4–6 weeks later.[297] Although ongoing exposure via direct contact with semen during unprotected sexual intercourse after conception is of low risk, the barrier method of contraception postconception may be considered.[265]

Apremilast. There are no available data for the impact of paternal exposure to apremilast on male fertility or pregnancy outcomes. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels threefold clinical exposure.[8]

Ciclosporin. There is no evidence that paternal use of ciclosporin affects male fertility; however, there are a paucity of studies on this.[265,298,299] Recent systematic reviews of cohort study data showed no impact on pregnancy outcomes.[265,298] This includes data from a Danish registry study of 247 children conceived during paternal use of ciclosporin, which found no association between paternal exposure to ciclosporin and increased risk of congenital abnormalities.[300]

Fumarates. A recent European consensus meeting concluded that contraception for males receiving fumarates is not required, although there is a paucity of evidence.[269]

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.	↑	Strong consensus[1] 100% agreement EXPERT CONSENSUS
We **suggest** stopping biologic therapy in the second and third trimester (except certolizumab pegol) to minimise fetal exposure and limit potential infection risk to the neonate.	↑	
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 national safety registries where available.	↑↑	

[1]Due to personal-financial conflict of interest 3 abstentions

Table 7 Overview of minimum time between stop of treatment and conception as given by respective SmPC

Infliximab	Adalimumab	Etanercept	Ustekinumab	Secukinumab	Apremilast*
6 months[133]	5 months[32]	3 weeks	15 weeks[88]	20 weeks[80]	No information provided in SmPC, 28 days advised by Celgene

Ixekizumab	Certolizumab	Brodalumab	Tildrakizumab	Guselkumab	Risankizumab
10 weeks	5 months*	12 weeks	17 weeks	12 weeks	21 weeks

*Certolizumab is the suggested biologic treatment option, for women who are planning conception or are pregnant and require a systemic therapy, see also respective chapters.

Methotrexate. Fertility—A recent systematic review identified 48 male exposures to methotrexate,[298] of which there were two isolated case reports of oligospermia (one reversible and one irreversible).[301,302] Another five publications comprising the remaining 46 exposures concluded that there was no impact of methotrexate on male fertility.[298] A case series of 26 men receiving methotrexate who had their semen examined using radioactive phosphorus for testicular histology and spermatogenic function showed no negative impact on fertility.[303] Another study compared semen parameters from ten men treated with methotrexate for severe psoriasis with those of ten men using topical steroids and found that those taking methotrexate were significantly more likely to have normal semen parameters.[304]

Pregnancy outcomes—Paternal methotrexate use has not been shown to cause teratogenicity or adverse pregnancy outcomes. A recent systematic review which reported 1511 periconception paternal methotrexate exposures concluded that there was no link between paternal methotrexate exposure and adverse pregnancy outcomes or congenital malformations.[298] The largest cohort studies, comprising national registry data[300,305,306] and longer-term outcomes,[307] showed no increased risk of paternal methotrexate exposure on pregnancy outcomes.

Although the above data do not support the need for any washout period for methotrexate, further evidence is required before this can be recommended. Recent EMA guidelines recommend discontinuing methotrexate for six months before attempting conception, which is a change from the previous recommendations of three months.[273] No evidence pertaining to the standard dose of methotrexate (5–30 mg/week) for inflammatory diseases is cited for this change of recommendation. The practice of the guideline group differs from this in favour of a shorter period of discontinuation (3 months).

Biologics. Although there are limited available data, cohort studies of TNF antagonists found no evidence for impairment in fertility during paternal use.[265,299] A systematic review highlighted that sperm motility and vitality may even improve under TNF antagonist therapy, possibly due to a decrease in disease activity.[308] Cohort studies (total of 60 exposures with outcome events documented in 28 cases) involving a range of TNF antagonists (adalimumab, certolizumab pegol, etanercept, infliximab) also demonstrated no evidence for an association between impaired pregnancy outcomes and paternal use of TNF antagonist therapy at the time of conception.[265,298,308]

There are no studies which have assessed the potential impact of paternal exposure to other biologic agents including IL-12/IL-

It is **recommended** that men discontinue methotrexate 3 months before attempting conception. * **EMA recommends 6 months as a means of precaution, the practice of the guideline group differs from this.*	↑↑	Strong consensus[1] 100% agreement EXPERT CONSENSUS
As a precaution, it is **suggested** that men receiving 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.	↑↑	

[1]Due to personal-financial conflict of interest 3 abstentions

23p40 inhibitors, IL-17 inhibitors or IL-23p19 inhibitors on male fertility or pregnancy outcomes.

3.13 Vaccinations: How should vaccinations in psoriasis patients on systemic treatment be managed?

A narrative literature review was conducted in November 2019.

Results/Answer In psoriasis patients, vaccination using dead vaccines and live vaccines can be performed at any time, unless a systemic treatment is given that necessitates a different strategy. Psoriasis on its own should not be considered a reason to deviate from standard vaccination recommendations.

Before initiating a systemic treatment, vaccination status should be checked and completed if possible. Annual flu vaccination and vaccination against pneumococci (age > 60) is particularly recommended. National recommendations for vaccination should be followed.[309]

When psoriasis patients receive any kind of systemic therapy dead vaccines can be given, however, vaccination responses may be decreased.

Therefore, it is recommended to use inactivated vaccines 2 weeks and attenuated live zoster vaccine 2–4 weeks prior to initiation of systemic therapy. If patients receiving systemic/immunosuppressive therapy, inactivated vaccines should be given without treatment interruption.[310]

Live vaccines (including measles–mumps–rubella, varicella) can be used in patients receiving acitretin, apremilast and fumarates. Live vaccines are contraindicated in psoriasis patients treated with ciclosporin and methotrexate, the tumour necrosis factor alpha (TNFa)-antagonists adalimumab, certolizumab, etanercept and infliximab, and the interleukin 17A-antibodies ixekizumab and secukinumab, and the interleukin 17RA-antibody brodalumab.

Generally, administration of a live vaccine after discontinuation of immunosuppressive therapy should be determined considering factors including its half-life (i.e. 5 half-lives) or mechanism of action. For the following medications, the respective SmPC provides recommendations with regard to timing is available:

Guselkumab: Wait two weeks after live vaccine, start vaccination 12 weeks after last dose.[311]

Risankizumab: Wait 4 weeks after live vaccine, start vaccination 21 weeks after last dose.[312]

Ustekinumab: Wait two weeks after live vaccine, start vaccination 15 weeks after last dose.[313]

Tildrakizumab: Wait four weeks after live vaccine, start vaccination 17 weeks after last dose.[314]

For live or live-attenuated vaccines in infants (up to 6 months of age) whose mothers received biologic therapy beyond 16 weeks' gestation, see chapter pregnancy.

3.14 Immunogenicity of targeted therapies in psoriasis

Narrative review of the existing literature was conducted.

Results/Answer A lack of fully comparable information on the formation of antidrug antibodies against targeted therapies in psoriasis has been identified in the course of the guideline's development. Within the scope of this version of the guideline, a thorough systematic search of the available evidence has not been feasible and a consensus on consequent measures has not been achieved. The author group acknowledges that there is evidence of a beneficial effect of the combination of methotrexate with adalimumab from psoriasis patients and MTX with infliximab in rheumatoid arthritis or Crohn's disease patients to reduce the formation in ADA.

The guideline group encourages researches to pursue further investigations into the field of antidrug antibodies and to generate data that allows comparison between different drugs and that can lead clinically relevant recommendations.

The authors encourage further opinion papers, narrative or preferably systematic reviews to further advance the discussion on immunogenicity.[315-318]

3.15 COVID-19: Guidance for systemic therapy of psoriasis during COVID-19 pandemic

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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