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POSITION STATEMENT

Practical recommendations for systemic treatment in psoriasis according to age, pregnancy, metabolic syndrome, mental health, psoriasis subtype and treatment history (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis; part 1)

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Abstract

Background Impressive progress in new therapeutic options has been made for psoriasis. Treatments include topical steroids, phototherapy, conventional, synthetic disease-modifying drugs and an expanding list of biologics.

Objective The primary objective of this work was to collect evidence for the creation of practice guidelines for systemic treatment of psoriasis (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis).

Methods Evidence-based recommendations were formulated using a quasi-Delphi methodology after a systematic search of the literature and a consensus procedure involving 8 psoriasis experts.

Results In this part, the use of systemic treatment in different age groups, during pregnancy, in metabolic syndrome, in patients with mental health problems, in different psoriasis subtypes and in previously systemically treated patients treatment is discussed.

Conclusion Guidance on therapeutic choice in specific clinical situations in psoriasis is provided in order to facilitate the decision-making in clinical practice.

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Conflict of Interest

Authors have no conflict of interest with regard to the topic of this manuscript.

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Introduction

The therapeutic arsenal of psoriasis has quickly risen to the widest of any inflammatory skin disease. While this is very promising for our patients, it complicates the 'right' personalized therapeutic choice of the clinician. Due to the vast amount of literature, it has even for psoriasis experts become almost impossible to be aware of all studies that might be relevant in each clinical context. Patient characteristics such as age, weight or comorbidities such as diabetes or cardiovascular diseases may interact with efficacy and/or development of adverse events. Special psoriasis subtypes such as nail psoriasis, pustular psoriasis and erythrodermic psoriasis require a different approach. Despite evidence of efficacy, some drugs are licensed in all age groups (e.g. children), and additionally, previous systemic drugs may influence the outcome of subsequent treatment.

The BETA-PSO (Belgian Evidence-based Treatment Advice in Psoriasis) project was initiated by the Royal Belgian Society of Dermatology and Venerology (under the presidency of Jo

Lambert, first author) with the intention to provide a practical aid for dermatologists to facilitate a well-informed therapeutic decision for each patient. Although the context and reimbursement criteria of Belgium were taken into account, these recommendations are likely to be valuable for all dermatologists treating psoriasis patients worldwide.

In this project, relevant clinical questions on the treatment of psoriasis were formulated and a systematic search was performed. Subsequently, a group of 8 Belgian psoriasis experts discussed the data, rated the evidence and made specific appropriate recommendations.

Material and methods

The clinical recommendations were developed using a quasi-Delphi consensus methodology as follows: an expert group (EG) of 8 Belgian dermatologists who treat patients with psoriasis, discussed and agreed on the recommendation of the type of systemic treatment which was considered to be advisable in a particular clinical context based on the existing evidence. The experts identified during a full-day face-to-face meeting on 16 January 2019 a list of 38 questions related to real-world situations frequently faced by clinicians when managing patients with psoriasis in their clinics.

Each expert was assigned a separate topic to summarize based on a systematic search of the literature in PubMed. Articles (including randomized controlled trials, case–control studies, observational studies, systematic reviews, meta-analyses, case reports but excluding letters and opinion papers) on psoriasis patients treated with systemic treatments for psoriasis (conventional, synthetic and biological) were included that reported data on:

1 the influence of metabolic comorbidities on the outcome (efficacy on psoriasis, side-effects) or the influence of the treatment on metabolic comorbidities
2 the influence of the treatment on specific clinical situations such as nail psoriasis, erythrodermic psoriasis and pustular psoriasis
3 the effect of being biological experienced or not
4 the influence of age on the outcome (efficacy, side-effects) and the specific use of the considered drugs in defined age groups (efficacy, side-effects)
5 the influence of the treatment on mental health

The following sixteen drugs for the systemic treatment of psoriasis were considered in this practical guidance:

- conventional antipsoriatic drugs: acitretin, cyclosporine, dimethylfumarate, methotrexate
- synthetic antipsoriatic drugs: apremilast
- biological antipsoriatic drugs: tumour necrosis factor (TNF) antagonists: adalimumab, certolizumab pegol, etanercept, infliximab; interleukin (IL) 12/23 inhibitor: ustekinumab; IL23/p19 inhibitors: guselkumab, risankizumab, tildrakizumab; IL17 receptor blocker: brodalumab; IL17 inhibitors: ixekizumab, secukinumab

Searches were performed on 27 November 2018 and were restricted to publications during previous 5 years, in English language. The search was simultaneously performed for all clinical situations (BETA-PSO part 1 and 2) (Figure S1 and Table S1). Additionally, SmPCs (Summary of Product Characteristics) of the concerned drugs were screened. An updated literature search was performed 25 January 2019.

The studies identified through electronic searches were subjected to screening of the title and abstracts to find relevant publications. During first pass, all the references were screened by single analyst as per specified population, intervention, comorbidities and outcome (PICO) criteria provided in Table 1.

In addition to a comprehensive literature search of the available published evidence, pharmaceutical manufacturers of treatments currently licensed in Belgium for the systemic treatment of psoriasis were invited to provide the latest peer-reviewed published materials on their drugs. The experts were allowed to add any additional relevant articles if deemed necessary (e.g. if published before 5 years).

The quality of the evidence (A: high, B: moderate and C: low) and the strength of the recommendations (strong vs weak) were categorized according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria.[1] A high level of evidence (A) was given for data from well-sized randomized clinical trials or extensive experience in clinical practice. Moderate evidence (B) was considered in case of observational studies, small-sized randomized clinical trials or moderate experience in clinical practice. Low evidence (C) was attributed when only case series, retrospective studies without controls were available or there was only limited experience in clinical practice.

The outcome of the identified studies was classified as indicating (i) that the efficacy of the drug was preserved without causing increased adverse events or worsening of the comorbidity; (ii) a limited risk of decreased efficacy of the drug and/or limited risk of increased adverse events or worsening of the comorbidity, (iii) a moderate risk of decreased efficacy of the drug and/or moderate risk of increased adverse events or worsening of the comorbidity and (iv) an important risk of decreased efficacy of the drug and/or moderate risk of increased adverse events or worsening of the comorbidity.

Subsequently, the 38 clinical questions were answered by each expert via an online digital platform. The participants were able to review all comments and the supporting published evidence. For each clinical situation, the experts agreed on a 'strong' or 'weak' recommendation in favour or against the use of the concerned systemic treatments. The consolidated answers generated were summarized into clinical recommendations and reviewed by the expert group. The experts were then invited to review wording of the draft clinical recommendations and to vote (agree/disagree) (8 March 2019 to 19 April 2019) concerning the final wording of the clinical

TABLE 1 Recommendations for systemic psoriasis treatments according to age and pregnancy/breastfeeding

Strong recommendation in favour "*Will be efficacious and cause no specific harm in this patient group*"	**Weak recommendation in favour** "*Will likely be efficacious and likely cause no specific harm in this patient group*"	**Weak recommendation against**: evaluate risk versus benefit case by case "*Might/may be less efficacious or might/may cause harm in this patient group*"	**Strong recommendation against** "*Likely to cause harm in this patient group*"	**Insufficient evidence to make a recommendation**
Children MTX ADA (>4 yr), ETA (> 6 yr) ACIT	CYCLO	FUM*	IFX	APR* CERTO* SEC*, IXE*, BROD* UST*, GUS*, RIS*, TIL*
Adolescents MTX, ACIT (♂), FUM ADA, ETA, IFX UST(> 12yr)	CYCLO		ACIT (♀)	APR* CERTO* SEC*, IXE*, BROD* GUS*, RIS*, TIL*
Elderly ACIT, MTX, CYCLO, FUM ADA, CERTO, ETA, IFX APR SECU, IXE, BROD UST, GUS				RIS, TIL
Pregnancy CERTO	ADA, ETA, IFX (not 3rd trim) UST(not 3rd trim) SEC (not 3rd trim)	CYCLO	ACIT (3 yrs before) FUM, MTX (6 mths before) APR	GUS, RIS, TIL IXE, BROD
Breastfeeding ADA, CERTO, ETA, IFX SECU, IXE, BROD UST, GUS, TIL, RIS			ACIT, MTX, CYCL, FUM APR	
Males wishing to conceive ACIT, CYCLO APR	FUM ADA, CERTO, ETA, IFX SECU, IXE, BROD UST, GUS, TIL, RIS		MTX (3 months before)	

ACIT, acitretin; ADA, adalimumab; APR, apremilast; BROD, brodalumab; CERT, certolizumab pegol; CYCLO, cyclosporin; ETA, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab.
†Unlicensed for this indication.

recommendations. Where there was disagreement with the draft wording, the chairperson contacted the expert to understand and clarify the issue. The recommendation was then amended on 17 September 2019 to all members' satisfaction and agreed upon via a final voting step (agree/disagree) on 10 January 2020.

Results

Clinical recommendations

Age *Paediatric patients.* In children below 12 years from an efficacy and safety perspective, we recommend that the following biological drugs, adalimumab and etanercept, and the conventional systemic drugs, methotrexate and cyclosporine (short-term use only), are used to treat paediatric psoriasis patients. Some advisors report good results with acitretin therapy in paediatric psoriasis patients, in doses of 0, 3–0 and 5 mg/kg. However, we advise caution when using acitretin due to occasional reports of bone changes in children using retinoids.[2] A far more recent review of bone toxicity of retinoids in psoriasis (albeit not in children) did not show evidence for bone toxicity.[3]

We do not recommend using infliximab in paediatric psoriasis patients due to higher reported rates of malignancies associated with infliximab use compared to the general paediatric population.[4]

Some reports mention the use of fumarates although it is currently not licensed in this age group in Belgium.[5]

Although there is evidence to show that the synthetic drug apremilast, the TNF inhibitor certolizumab pegol, the IL17 inhibitors, brodalumab, ixekizumab and secukinumab; the IL12/23 inhibitor ustekinumab (and other new biological

drugs such as the IL23/p19 inhibitors: guselkumab, risankizumab, tildrakizumab) are efficacious in paediatric patients, we are – due to a lack of safety data – unable to recommend their use in paediatric psoriasis patients at this point in time. We also note that these drugs are not currently licensed for use in this age group.

Based on the manufacturers' information, we note that the following age limits apply: adalimumab is recommended for the treatment of psoriasis patients above 4 years and etanercept in patients above 6 years of age.[6,7]

Adolescent patients. In young people with psoriasis, from an efficacy and safety perspective, we recommend the biological drugs, adalimumab, etanercept, infliximab and ustekinumab, and the conventional drugs acitretin, cyclosporine (for short-term use only), fumarates and methotrexate, for the treatment of adolescent patients, 12–18 years.

However, we do not recommend acitretin in adolescent girls with psoriasis due to the risk of teratogenicity and the need for contraception for 3 years following stopping acitretin treatment.

Similar to paediatric patients, apremilast, the TNF inhibitor certolizumab pegol, the IL17 inhibitors, brodalumab, ixekizumab and secukinumab, and the IL23/p19 inhibitors, guselkumab, risankizumab and tildrakizumab, can currently not be recommend in these patients due to limited data and lack of licence for use in children.

Based on the manufacturers' information, we note that the following age limits apply: ustekinumab is recommended for the treatment of psoriasis patients greater than 12 years.[8]

Elderly patients. From a safety and efficacy perspective in elderly psoriasis patients, we recommend the following biological drugs adalimumab, certolizumab pegol, etanercept and infliximab; brodalumab, ixekizumab and secukinumab; ustekinumab, guselkumab, risankizumab, tildrakizumab and, the synthetic drug, apremilast.

We also recommend the conventional drugs, methotrexate, cyclosporine, and fumarates and acitretin are used to treat patients (greater than 65 years) with psoriasis.

Pregnancy/Lactation *Female patients of childbearing age.* - Based on the available placental transfer and pregnancy outcomes evidence, our recommendation for female patients with psoriasis wishing to conceive or who may be pregnant and where treatment is clinically needed is to use of the Fc-free biological drug certolizumab pegol as first-line treatment, followed by either adalimumab or etanercept.[9–11]
However, the use of Fc-containing biologics (including etanercept, adalimumab) during the third trimester is not recommended. We also advise that infliximab, secukinumab, ixekizumab, brodalumab and ustekinumab may be used in female patients wishing to conceive; however, data are limited with these biological drugs.[12–14]

Regarding the conventional drugs, cyclosporine should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.[15] We also recommend that female psoriasis patients who may wish to conceive to have completed acitretin treatment at least 3 years before conception due to the high teratogenicity risk associated with this drug. Likewise, we advise female patients to complete treatment with fumarates and methotrexate for at least 6 months before conception.[16,17] Regarding the newer biological drugs, we note from the manufacturer's information that pregnancy should be avoided for 17 weeks after treatment with tildrakizumab, for 12 weeks with guselkumab and for 21 weeks with risankizumab.[18] Finally, apremilast is contraindicated in female psoriasis patient wishing to conceive or who may be pregnant. This is based on animal data indicating apremilast can cause foetal loss in mice and monkeys.[19]

Breastfeeding. From a safety perspective, we advise that the majority of the biological drugs may be safely used to treat female psoriasis patients who are also breastfeeding, as they are denatured in the gastro-intestinal tract of the infant.[20]

Apremilast, and fumarates, methotrexate, cyclosporine and acitretin are contraindicated during lactation due to adverse risk posed to the feeding infant. Therefore, we recommend that they should be avoided while breastfeeding.

Males wishing to conceive. From a safety perspective, we recommend that cyclosporine, acitretin and apremilast and fumarates can be used to treat male psoriasis patients who are wishing to conceive. The only formal contraindication is methotrexate with a recommendation to stop 6 months prior to conception. However, this is not evidenced by clear data on paternal-mediated teratogenicity.[21]

On the use of biologics (TNF inhibitors, IL17 blockers, IL17 receptor blocker and IL23 blockers) in males wishing to conceive, there is currently no clear evidence pointing to an increased risk.[22]

Mental health *Psychiatric disorders.* Patients with psoriasis are more affected by depression, anxiety, suicidal ideation behaviour (SIB), lack of confidence, insomnia and poor quality of life (QOL), and we also know that these symptoms are reduced with effective treatment in these patients.[23] Therefore, we recommend that the rapidity of onset of action with effective treatment to improve the QOL in psoriasis patients with psychiatric issues may be an advantage. Large studies showed a sustained benefit of biologics in reducing antidepressant use among psoriasis patients. The beneficial effect was more significant with continuous treatment.[24,25] Biological treatments seem more effective in

reducing depression and insomnia than DMARDs.[24,26] However, there is a lack of robust comparative data between the different biological drugs. Although adalimumab, etanercept and ustekinumab were associated with a statistically significant reduction in depressive symptoms, comparison between the drugs could not be made due to different rating scales being used.[27] One study found greater improvements in anxiety and depression with guselkumab vs adalimumab.[23] Studies have shown that the IL-17 antagonists, secukinumab and ixekizumab improve patients' QOL and alleviate depression in 40% patients, respectively.[28,29] Fumarates have also been shown to reduce depressive symptoms in patients.[30]

The TNF antagonists: infliximab, adalimumab, certolizumab pegol and etanercept; the IL12/23 inhibitor: ustekinumab; the IL23/p19 inhibitors: guselkumab, risankizumab and tildrakizumab; the IL17 inhibitors: secukinumab and ixekizumab; and conventional drugs, including methotrexate, cyclosporin, fumarates and acitretin, have been shown to be effective when used as systemic treatments for psoriasis patients with psychiatric issues such as depression.

Although the AMAGINE studies also confirm the improvement of patients' quality of life with brodalumab, we would advise caution, however, when using the IL17 receptor blocker, brodalumab, in patients with a history of depression as suicidal behaviour has been reported in patients treated with an FDA-mandated black box warning regarding suicide.[31] However, the EMA, Health Canada and the FDA, as well as recent reports, cannot confirm a causal relationship between brodalumab and suicidal ideation and behaviour.[32] We would also advise caution using the synthetic drug, apremilast, due to an increased risk of psychiatric disorders. Despite several studies showing an improvement in patients' QOL with treatment, an increased risk of mental disorders has been associated with its use in psoriasis patients.[33–35] The risks and benefits of starting or continuing treatment with apremilast should be carefully assessed whether patients report previous or existing psychiatric symptoms or whether concomitant treatment with other medicinal products likely to cause psychiatric events is intended.[19]

Metabolic disorders *Metabolic syndrome.* We advise that the TNF antagonists: adalimumab, certolizumab pegol, etanercept and infliximab; the IL12/23 inhibitor: ustekinumab; the IL23/p19 inhibitors: guselkumab, risankizumab and tildrakizumab; the IL17 receptor blocker: brodalumab; the IL17 inhibitors: ixekizumab and secukinumab; as well as the synthetic small molecule drug, apremilast, and the conventional drugs, methotrexate, cyclosporine, fumarates and acitretin can all be used as systemic treatments for adult psoriasis patients with metabolic syndrome. This is primarily because they provide effective treatment to reduce the symptoms of psoriasis and improve patients' quality of life. Secondly, some of the drugs might also offer some beneficial impact on the cardiovascular risk factors associated with the metabolic syndrome.[36]

There is currently an ongoing debate concerning improvement in physiological measures of metabolic syndrome resulting from various newer treatments such as TNF inhibitors for psoriasis. In fact, weight may increase in patients with their use.[37] Specifically, with cyclosporine treatment, atherogenic dyslipidaemia, arterial hypertension and glucose intolerance may worsen, and with acitretin use, atherogenic dyslipidaemia may worsen. In patients with increased risk for liver or renal toxicity, caution is also recommended for methotrexate.[38] Therefore, we recommend careful monitoring and follow-up of patients treated with these drugs.

We also advise increased surveillance of the markers of metabolic syndrome in psoriasis patients including increasing waistline, elevated blood pressure, raised triglyceride levels, reduced HDL cholesterol and raised fasting glycemia. We also advise patients with metabolic syndrome receive obesity management and smoking cessation advice, as relevant.

Type II diabetes and/or insulin resistance. From a safety perspective, none of the biological and non-biological systemic treatments available for patients with psoriasis are specifically contraindicated in those patients who also have type 2 diabetes and/or insulin resistance. It is difficult to make meaningful clinical recommendations due to a lack of comparative data between these drugs. Some studies suggest that the use of anti-TNF drugs, such as infliximab, adalimumab, certolizumab pegol and etanercept, is associated with decreased insulin resistance.[39–41] Another study, however, has shown no benefit with anti-TNF drugs in combination with methotrexate versus methotrexate alone on HbA1C or fasting blood glucose in psoriasis patients.[42] Methotrexate and acitretin have also been linked to a decreased insulin resistance in psoriasis.[43] We do advise caution with the use of cyclosporine and methotrexate in these patients due to an increased risk of liver and renal toxicity.[38]

All of the systemic treatments considered can be used to treat psoriasis patients who also have type 2 diabetes and/or insulin resistance. We advise that the TNF antagonists: adalimumab, certolizumab pegol, etanercept and infliximab; the IL12/23 inhibitor: ustekinumab; the IL23/p19 inhibitors: guselkumab, risankizumab and tildrakizumab; the IL17 receptor blocker: brodalumab; the IL17 inhibitors: ixekizumab and secukinumab; as well as the synthetic drug, apremilast, and the conventional drugs, fumarates and acitretin, can be used as systemic treatments for psoriasis patients with type II diabetes and/or insulin resistance. Cyclosporine and methotrexate can also be used although more caution is advisable.

Obesity. For obese psoriasis patients, we advise that the TNF antagonists: adalimumab, certolizumab pegol, etanercept and

infliximab; the IL12/23 inhibitor: ustekinumab; the IL23/p19 inhibitors: guselkumab, risankizumab and tildrakizumab; the IL17 receptor blocker: brodalumab; the IL17 inhibitors: ixekizumab and secukinumab; as well as the synthetic drug, apremilast, and the conventional drugs, fumarates and acitretin, be used as systemic treatments. Diet interventions should be encouraged as they result in improved treatment outcomes using biologic therapy.[44]

From an efficacy perspective, studies have shown that the biological drugs, ustekinumab, infliximab, adalimumab and etanercept, and most conventional drugs require higher dosing in obese psoriatic patients, compared with healthy-weight patients. Therefore, it is our opinion that weight-adjusted dosing with these drugs may be required in obese patients. Currently, only infliximab and ustekinumab allow a specific higher dosing by weight.[45,46] Nonetheless, this trend is not yet clear with the newer biologics. Latest trial data on risankizumab, guselkumab, ixekizumab and brodalumab show a less pronounced effect of weight on their efficacy.[47–50] A few studies have reported an increase in weight associated with treatment with some of the biologics (such as TNF antagonists) although results remain contradictory to date.[51,52] Apremilast rather leads to weight loss.[53]

From a safety perspective, we advise caution, however, with weight-dependent dosing of the conventional drugs, methotrexate and cyclosporine, due to increased risk of renal and liver toxicities associated with increased dosing.

Cardiovascular risk factors. It is well known that psoriasis patients have an elevated risk of atherosclerosis, characterized by endothelial dysfunction. The features of metabolic syndrome, including hypertension and dyslipidaemia, are associated with endothelial activation in patients with moderate-to-severe psoriasis.

In patients with psoriasis and cardiovascular risk factors, we advise that the biologics including adalimumab, certolizumab pegol, etanercept and infliximab; ustekinumab; guselkumab, risankizumab and tildrakizumab; brodalumab; ixekizumab and secukinumab; as well as the synthetic drug, apremilast, and the conventional drugs, including cyclosporine, methotrexate, fumarates and acitretin, can be used from an efficacy and safety perspective as systemic treatment.

We suggest that the TNF antagonist drugs are primarily used to treat psoriasis patients with cardiovascular risk factors. Studies show that adalimumab therapy leads to a reduction in the endothelial activation biomarker, soluble (s) E-selectin (sE-selectin) levels, and a decrease in intima–media thickness as an indicator of atherosclerosis has been reported.[54,55] Nonetheless, only few preliminary findings suggest a clinical significance.[56] No difference in cardiovascular events or atrial fibrillation was found between TNFi therapy and ustekinumab was found in a large cohort study.[57] There is also evidence to suggest that the anti-IL17 drug, secukinumab, might have a beneficial effect on CV risk by improving the endothelial function of patients with psoriasis.[58] A recent observational study shows that biologic therapy in severe psoriasis was associated with favourable modulation of coronary plaque indices by coronary computed tomography angiography.[59] These findings highlight the importance of systemic inflammation in coronary artery disease and larger, randomized trials with all the biological drugs are required.

We advise caution with cyclosporine and acitretin treatment in psoriasis patients with cardiovascular risk factors as they have been shown to increase the risk of hypertension and dyslipidaemia, and hyperlipidaemia alone, respectively. However, these side-effects are manageable with appropriate treatment and should not form a formal contraindication for its use.

We note that several of the anti-TNF drugs are contraindicated in psoriasis patients with moderate or severe heart failure (NYHA class III/IV) including adalimumab, certolizumab pegol and infliximab and that the entire class should be used with caution in patients with mild heart failure (NYHA class I/II).

Non-alcoholic fatty liver disease. From an efficacy and safety perspective, most biological and non-biological systemic drugs for psoriasis can be used effectively to treat psoriasis patients who also have non-alcoholic fatty liver disease. However, there is no evidence to show whether one of the listed drugs is more or less efficacious compared with another in a patient with psoriasis and fatty liver disease. This is due to a lack of comparative studies between the drugs in this patient group.

In psoriasis patients with non-alcoholic fatty liver disease, we recommend that the biological drugs, infliximab, adalimumab, certolizumab pegol and etanercept; ustekinumab, guselkumab, risankizumab and tildrakizumab; brodalumab, ixekizumab and secukinumab; the synthetic drug, apremilast; and the conventional drug, cyclosporine, are used from an efficacy and safety perspective.

From a safety perspective, methotrexate has been shown to cause elevated liver function tests in patients. Caution is warranted with methotrexate but also with fumarates and acitretin. This is because methotrexate has been shown to increase liver function tests in these patients, although no cases of liver failure have been observed with methotrexate treatment.[60] Several cases of liver toxicity have been described with fumarates in patients with multiple sclerosis although severe liver injury has not been reported in psoriasis.[61,62] Regarding acitretin, serum aminotransferase elevation has been noted, but is usually self-limiting.[63]

Psoriasis subtypes *Nail psoriasis.* From an efficacy perspective, we recommend in psoriasis patients with nail disease the TNF antagonists: infliximab, adalimumab, certolizumab pegol and etanercept; the IL12/23 inhibitor: ustekinumab; the IL23/p19 inhibitors: guselkumab and risankizumab; the IL17 receptor blocker: brodalumab; the IL17 inhibitors: ixekizumab and

secukinumab; and the synthetic drug, apremilast.[64–67] Also, the conventional drugs dimethylfumarate, cyclosporine and methotrexate are used based on clinical trial data. There is less robust evidence supporting the use of the conventional drugs cyclosporin, methotrexate and acitretin; however, it is our opinion that these drugs also provide benefit to psoriasis patients with nail disease especially in patients with limited skin involvement (PASI/BSA < 10).[68] There is also limited evidence supporting the use of dimethylfumarate.[69] There was no recommendation of the experts on the use of tildrakizumab in these patients, mainly due to a paucity of supporting data.

Generalized pustular psoriasis (GPP). We recommend the use of acitretin for the treatment of patients with generalized pustular psoriasis (GPP), as it is the only drug licensed for this indication. There is also evidence supporting the use of methotrexate, adalimumab, ixekizumab, secukinumab, brodalumab and guselkumab to treat GPP patients and, based on our collective experience, we advise their use in these patients.[70–74] There is less robust evidence based on limited case series and case reports supporting the use of infliximab, etanercept, ustekinumab, risankizumab, tildrakizumab, apremilast and cyclosporine in GPP patients.[75,76] We do not recommend the use of fumarates in the systemic treatment of GPP patients, due their slow mode of action and potential hypersensitivity reactions worsening the disease.

Erythrodermic psoriasis. We agree that cyclosporine and infliximab appear to be the most rapidly acting agents for the treatment of erythrodermic psoriasis. Acitretin and methotrexate are also appropriate first-line choices, although they usually work more slowly.[77]

There is also clinical evidence supporting the use of the biological IL12/23 inhibitor, ustekinumab for the treatment of erythrodermic psoriasis.[78,79] Beneficial results with secukinumab, ixekizumab, brodalumab, guselkumab, adalimumab, etanercept, apremilast and cyclosporine have been observed to treat erythrodermic psoriasis patients. However, this is based on some published open-label studies and case series mostly in Japanese patients.[72–74,80] Based on our collective experience, we advise their use. No data on use of risankizumab nor tildrakizumab were found.

We do not recommend the use of fumarates, however, in the systemic treatment of erythrodermic psoriasis patients, due to their slow mode action and potential hypersensitivity reactions worsening the disease.

Practical use of biologics *Biologic-experienced patients.* In biologic-experienced patients, drug survival is better if switch is performed between as opposed to within biologic classes.[81] However, in case a deliberate choice was made for a certain biologic class based on efficacy, side-effects or comorbidities, evidence indicates that switch within class is also a good option if a biologic with a higher efficacy is chosen.[82] The general consensus of the expert discussion was to consider a switch to another biologic class or to opt for the biologic within the same class exhibiting the highest efficacy in clinical trials. Overall, recent data suggest that newer biologics are less affected by a history of previous failure to another biologic.[83]

Intermittent treatment. Regarding biologics, we recommend continuous systemic treatment for patients with psoriasis when the patient is still receiving benefit. Should a psoriasis patient wish to stop and then restart systemic treatment, we advise that it is possible to do so, particularly with etanercept and ustekinumab.[84,85] Conventional drugs and synthetic drug apremilast seem well suited for intermittent treatment. There is robust evidence that demonstrates these drugs can be stopped and then restarted with equivalent efficacy and without increased risk of flare of disease. For adalimumab, certolizumab pegol, guselkumab, risankizumab and tildrakizumab, ixekizumab, secukinumab and brodalumab, the evidence is less clear. Fumarates can also be used intermittently although they exhibit a slow onset of action.[86] This observation is based on our collective opinion and experience.

There is currently insufficient evidence to support stopping and then restarting treatment with other biological drugs, including adalimumab, certolizumab pegol and tildrakizumab. We advise caution with this approach until these data are available. For guselkumab, risankizumab, ixekizumab and secukinumab, promising results when retreating after drug withdrawal were obtained in clinical trial settings indicating that intermittent treatment might be an option with the newer IL23/p19 inhibitors and IL17 blockers.[87,88]

However, we recommend against stopping and restarting infliximab due to reduced efficacy on restarting treatment as a result of the development of antidrug antibodies. From a safety perspective, there is also an increased risk of serious infusion reactions with intermittent infliximab dosing.[46,89]

Use of biosimilars. From an efficacy and safety perspective, we advise that it is possible to switch from TNF antagonist reference drugs, infliximab, adalimumab and etanercept, to their respective biosimilar.[90] However, this advice is based on some but not all of the groups' experience with switching.

Discussion

Systemic psoriasis treatments result in a variable clinical efficacy and adverse event rate depending on pre-existing patients' characteristics. The decision aid based on the current evidence in Tables 1, 2 and 3 can be a valuable tool in clinical practice to guide the therapeutic choice. Unfortunately, evidence is in a substantial part limited to 'level C', indicating case series, case reports or limited experience in clinical practice. In case of new biologics, data are often still lacking. Head-to-head comparison

TABLE 2 Recommendations for systemic psoriasis treatments according to comorbidities, psoriasis subtypes and intermittent treatment

Strong recommendation in favour *"Will be efficacious and cause no specific harm in this patient group"*	Weak recommendation in favour *"Will likely be efficacious and likely cause no specific harm in this patient group"*	Weak recommendation against: evaluate risk versus benefit case by case *"Might/may be less efficacious or might/may cause harm in this patient group"*	Strong recommendation against *"Likely to cause harm in this patient group"*	Insufficient evidence to make a recommendation
Psychiatric disorders ACIT, MTX, CYCLO, FUM ADA, CERT, ETA, IFX UST, GUS, RIS, TIL SEC, IXE		APR BROD		
Metabolic syndrome FUM APR ADA, CERT, ETA, IFX UST, GUS, RIS, TIL SEC, IXE, BROD	ACIT, MTX, CYCLO			
Diabetes or insulin resistance ACIT, FUM APR ADA, CERT, ETA, IFX UST, GUS, TIL, RIS SEC, IXE, BROD	MTX, CYCLO			
Obesity FUM APR IFX UST IXE, BROD RIS, GUS,	ADA, CERT, ETA SEC TIL	ACIT, MTX, CYCLO		
Cardiovascular risk factors MTX, FUM, APR ADA, CERT, ETA, IFX (case without heart failure) SEC, IXE, BROD UST, GUS, TIL, RIS		ACIT, CYCLO	ADA, CERT, ETA, IFX (case with heart failure)	
Non-alcoholic fatty liver disease CYCLO APR ADA, CERT, ETA, IFX UST, GUS, RIS, TIL SECU, IXE, BROD		ACIT, MTX, FUM		
Nail psoriasis ACIT APR, CYCLO, MTX, FUM ADA, CERT, ETA, IFX UST, GUS , RIS BROD, IXE SEC				TIL
Generalized pustular psoriasis ACIT, MTX ADA SEC, IXE, BROD GUS	APR, CYCLO ETA, IFX UST, RIS		FUM	CERT TIL

Table 2 *Continued*

Strong recommendation in favour *"Will be efficacious and cause no specific harm in this patient group"*	Weak recommendation in favour *"Will likely be efficacious and likely cause no specific harm in this patient group"*	Weak recommendation against: evaluate risk versus benefit case by case *"Might/may be less efficacious or might/may cause harm in this patient group"*	Strong recommendation against *"Likely to cause harm in this patient group"*	Insufficient evidence to make a recommendation
Erythrodermic psoriasis				
ACIT, MTX, CYCLO IFX UST	ADA, ETA, CYCLO APR GUS SECU, IXE, BROD		FUM	TIL, RIS
Intermittent treatment				
ACIT, MTX CYCLO APR ETA UST	GUS, RIS, TIL SEC, IXE	FUM ADA, CERT, BROD	IFX	

ACIT, acitretin; ADA, adalimumab; APR, apremilast; BROD, brodalumab; CERT, certolizumab pegol; CYCLO, cyclosporin; ETA, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab.
Green: will be efficacious and cause no specific harm in this patient group; Light green: will likely be efficacious and likely cause no specific harm in this patient group; Orange: might/may be less efficacious or might/may cause harm in this patient group; Red: likely to cause harm in this patient group; Grey: insufficient evidence to make a recommendation.

Table 3 Evidence of systemic treatments for psoriasis in different clinical conditions

	ACITR	CYCLO	MTX	FUM	APR	IFX	ETA	ADA	CERT	UST	GUS	RIS	TIL	SECU	IXE	BRO
Pediatric psoriasis	A	A	A	C	C	C	A	A	NA	A	NA	NA	NA	NA	NA	NA
Adolescent	A	A	A	C	B	A	A	A	C	A	C	C	C	C	C	C
Elderly with psoriasis	A	A	A	B	B	B	B	B	B	A	B	B	B	A	B	B
Pregnancy/lactation	A	B	B	C	C	B	B	B	B	B	C	C	C	B	C	C
Depression	C	C	B	B	A	B	A	A	NA	A	A	C	NA	A	A	A
Metabolic Syndrome	B	B	B	B	A	A	A	A	A	A	A	A	A	A	A	A
Dyslipidemia	A	A	A	C	A	A	A	A	C	A	NA	NA	A	A	A	NA
Diabetes/Insulin Resistance	B	B	B	B	A	A	A	A	A	A	A	A	A	A	A	A
Obesity	C	B	B	B	A	A	A	A	NA	A	A	A	A	A	A	A
Hypertension	B	A	B	C	A	C	C	C	NA	A	NA	NA	A	C	C	NA
NAFLD/NASH	C	B	A	NA	A	C	C	C	NA	A	NA	NA	NA	C	NA	NA
Nail psoriasis	B	B	A	A	A	A	A	A	A	A	A	A	NA	A	A	A
Pustular psoriasis	C	C	C	NA	NA	C	C	C	NA	C	C	C	NA	C	C	C
Erythrodermic psoriasis	C	B	C	NA	NA	B	C	C	NA	C	C	NA	NA	C	C	C
Efficacy in biol experienced	C	C	C	C	C	C	C	B	B	B	B	B	B	B	B	A
Stopping and restarting	B	B	B	B	B	A	A	A	A	A	A	A	A	A	A	B
Switch to biosimilar	NA	NA	NA	NA	NA	B	B	B	NA	NA	NA	NA	NA	NA	NA	NA

Levels of evidence: A (high level of evidence), B (moderate level of evidence), C (low level of evidence).
Results of the studies: 1. *Green*: preserved efficacy without increased adverse events or worsening of the comorbidity; 2. *Yellow*: limited risk of decreased efficacy and/or limited risk of increased adverse events or worsening of the comorbidity, 3. *Orange*: moderate risk of decreased efficacy and/or moderate risk of increased adverse events or worsening of the comorbidity, 4. *Red*: important risk of decreased efficacy and/or moderate risk of increased adverse events or worsening of the comorbidity.
ACIT, acitretin; ADA, adalimumab; APR, apremilast; BROD, brodalumab; CERT, certolizumab pegol; CYCLO, cyclosporin; ETA, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab.

of drugs is very limited, especially in less common disease presentations such as generalized pustular psoriasis. Nonetheless, obvious 'red' and 'orange' flags should be recognized by every physician before a treatment is initiated.

Regarding age, many drugs are not licensed for use in children such as ustekinumab (>12 years), fumarates or apremilast (>18 years). Some experts chose acitretin as first choice in order to avoid long-term immunosuppressive effects despite the concern of bone changes based on data with long-term use of etretinate.[2] Older age, pre-existing renal or liver injury may increase the risk of adverse events of conventional drugs such as methotrexate and cyclosporin.[91] Furthermore, the risk of drug–drug interactions is increased in (elderly) patients with polypharmacy using methotrexate or cyclosporine and apremilast.[19,92]

In metabolic syndrome, several conventional drugs including cyclosporine, acitretin and methotrexate exhibit an unfavourable effect on lipids, hypertension and liver injury. However, as most issues are manageable by accurate intervention (e.g. diet, statins, antihypertensive medication), this does not preclude their use. Nonetheless, apremilast and biologics seem often a more favourable choice in patients with metabolic syndrome.

No clear data have shown a convincing different response of systemic treatments in nail psoriasis compared to psoriasis vulgaris. However, a BSA and/or PASI> 10 is often not reached in patients with nail psoriasis limiting the use of biologics in these patients. In Belgium, an extensive BSA involvement is not a requirement for reimbursement of fumarates which makes it a reasonable option despite limited reports on nail psoriasis.

Pustular and erythrodermic psoriasis display a different disease pattern requiring a tailored approach. Acitretin is the only licensed drug in generalized pustular psoriasis, although often combination therapy with corticosteroids is necessary, and it is contraindicated in women of childbearing age. Regarding erythrodermic psoriasis, one expert raised the concern of the differential diagnosis with cutaneous T-cell lymphoma. In the latter case, acitretin may be the safest option until the final diagnosis is established.

A limitation of these recommendations is that only the viewpoint of dermatologists was taken into account. The expert group emphasized the need for a multidisciplinary approach in patients with important comorbidities. These guidelines do not replace the need for shared decision-making as patients may balance efficacy versus side-effects differently.

Given the rapid evolution of the therapeutic landscape of psoriasis, readers should be aware that this project is a living guideline that will require a regular update based on new data. This is certainly the case for the new class of specific IL-23 inhibitors which have currently limited available data.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for screening and selection of the literature search in patients with psoriasis.
Table S1. Eligibility criteria for study screening.