POSITION STATEMENT

Practical recommendations for systemic treatment in psoriasis in case of coexisting inflammatory, neurologic, infectious or malignant disorders (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis; part 2)

J.L.W. Lambert,1,* S. Segaert,2 P.D. Ghislain,3 T. Hillary,4 A. Nikkels,5 F. Willaert,6 J. Lambert,7 R. Speeckaert1
1Department of Dermatology, Ghent University Hospital, Ghent, Belgium
2Private Practice, Tremelo, Belgium
3Dermatology, Cliniques Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
4Dermatology, University Hospital Leuven, Leuven, Belgium
5Dermatology, Centre Hospitalier Universitaire de Liège, Liège, Belgium
6Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
7Dermatology, University Hospital of Antwerp, Antwerp, Belgium
*Correspondence: J.L.W. Lambert. E-mail: jo.lambert@uzgent.be

Abstract

Background Psoriasis patients carry an increased risk for associated comorbidities. Dermatologists have to be aware of the effects of systemic treatments not only on psoriasis but also on co-occurring diseases. In case of other coexisting inflammatory diseases, the right psoriasis treatment may improve both disorders. For infectious and malignant disorders, some treatments have to be avoided as they may be harmful.

Objective The primary objective of this project 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 eight psoriasis experts.

Results Recommendations are given on the use of systemic treatment in psoriatic arthritis, inflammatory bowel disease, demyelinating disorders, hepatitis B and C, HIV and cancer.

Conclusion This expert opinion is a practical guide for dermatologists when handling psoriasis patients with these specific conditions.

Received: 2 February 2020; Accepted: 15 May 2020

Conflicts of interest

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

Funding sources

Funding for this project was provided to the Royal Belgian Society of Dermatology and Venereology by six pharmaceutical companies: Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis and UCB. These companies were however not involved in the making of the manuscript.

Introduction

Psoriasis is associated with several other diseases which may or may not share pathogenic similarities. Coexisting disorders should be taken into account when initiating a systemic treatment. The most common associated disorder is psoriatic arthritis which may be present in up to 25% of psoriasis patients.1 Unfortunately, not all treatments are equally effective for both joints and skin requiring dermatologic-rheumatologic team work.

Inflammatory bowel disease is more prevalent in psoriasis patients. A meta-analysis found a relative risk in patients with psoriasis for Crohn’s disease and ulcerative colitis of 2.53 and 1.71, respectively.2 TNF-blockers have become one of the cornerstones of the management of inflammatory bowel disease. More recently, the IL-12/23 pathway has also been targeted. Encouraging results have been obtained with ustekinumab blocking both IL12 and IL23, while monoclonal antibodies
targeting only IL23 are also promising and entering phase II and III trials. In contrast, IL-17 blockade is ineffective in Crohn’s disease and may cause disease exacerbations. Anti-IL-17 treatment was linked to a nearly 3-fold increase of IBD in patients with chronic inflammatory diseases indicating that patients at risk for IBD should be identified in advance.6

Studies investigating a link between psoriasis and demyelinating diseases such as multiple sclerosis and Guillain–Barré are inconsistent and conflicting. While some small studies and case reports have suggested an increased risk, larger studies were unable to confirm this finding. The role of TNF in demyelinating disorders is yet incompletely understood, and several cases developing multiple sclerosis and Guillain–Barré in patients receiving TNF-blockers have been reported.7

As psoriasis requires a long-term treatment, patients with a history of malignancy or developing cancer during systemic psoriasis treatment are a relatively frequent event. Psoriasis patients carry an increased risk for different types of cancer and cancer mortality especially from liver, oesophageal and pancreatic cancer and lymphoma.8 In general, both conventional and newer treatments for psoriasis do not seem to result in a marked increased rate of malignancy. Nonetheless, in cancer patients the preservation of an effective antitumoral response is crucial and in general exceeds the importance of clearing the skin disease. Similarly in hepatitis or HIV, systemic treatments may worsen the infectious load and cause drug–drug interactions with antiviral treatments. In this article, practice guidelines for managing psoriasis patients with these coexisting disorders are proposed.

Material and methods

For the methodology, we refer to Part 1 of the BETA-PSO project. In Part 2, each expert was again assigned a separate topic to summarize based on a systematic search of the literature in PubMed. Articles (including RCTs, 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 Coexisting inflammatory conditions such as psoriatic arthritis and inflammatory bowel disease
2 Chronic infections like HIV, hepatitis or tuberculosis
3 Specific neurological conditions like demyelinating disease
4 The influence of the treatment on malignancies (including new-onset malignancies during/after treatment or treatment in patients with previous malignancies)

The definition of recommendations (strong vs. weak; in favour or against) was adapted compared to Part 1 and was different in the group of coexisting inflammatory diseases compared to infectious/malignant disorders. In inflammatory diseases, a weak recommendation in favour was considered in case the drug might be beneficial for the inflammatory disorder. In contrast, a weak recommendation in favour in case of infectious or malignant disorders was assigned in case the drug is (likely) not beneficial but also not harmful for the infection or malignancy.

Results

Clinical recommendations

Psoriatic arthritis (PSA) Several different classes of biological and non-biological drugs including TNFα antagonists, ustekinumab, IL17 inhibitors, as well as some non-biological and conventional drugs, are licensed both to treat psoriasis and psoriatic arthritis (PSA).

In psoriasis patients with psoriatic arthritis, we recommend methotrexate, apremilast and the following biological drugs: adalimumab, certolizumab pegol, etanercept and infliximab; ustekinumab; secukinumab and ixekizumab. They are not only effective in treating psoriasis but also alleviate the symptoms of PSA.

It is our expert opinion that other biologics including guselkumab, risankizumab, tildrakizumab and brodalumab are also effective treatment in psoriatic patients with PSA, although they are currently unlicensed in this indication.

Systemic treatment with cyclosporine, for psoriasis patients with PSA, is less advisable due to limited evidence. Nonetheless, some studies support beneficial effects of cyclosporine on the symptoms of PSA in patients with skin psoriasis. We do not recommend using the conventional drugs acitretin and fumarates in psoriasis patients with PSA as they are not indicated for the treatment of PSA. One study showed improvement of PSA with fumarates although confirmatory data are missing. There is no clinical or theoretical evidence to support benefit of PSA using acitretin.

Inflammatory bowel disease (IBD) Inactive IBD. In psoriasis patients with inactive IBD, we recommend that the TNF antagonists: adalimumab, certolizumab pegol and infliximab; the IL12/23 inhibitor: ustekinumab; the IL17 inhibitors: secukinumab, risankizumab and tildrakizumab; as well as the synthetic drug apremilast, and the conventional drugs, methotrexate, cyclosporine, fumarates and acitretin, can all be used as systemic treatments as they also have a beneficial or neutral effect on IBD symptoms.

We advise caution with use of the following anti-IL17 biological drugs: secukinumab, ixekizumab and brodalumab, to treat psoriasis patients with inactive IBD, and in those patients with a family history of IBD. We also advise not using etanercept in these patients due to the possibility of a flare-up of IBD symptoms.

Active IBD. We recommend the following systemic biological drugs are used to treat psoriasis patients who also have active inflammatory bowel disease (IBD): adalimumab and infliximab. This is because these TNFα antagonists are licensed for the treatment of both psoriasis and inflammatory bowel disease.
also advise the use of certolizumab pegol as it is beneficial in these patients despite not being licensed for IBD in Europe.19

The IL12/23 inhibitor, ustekinumab, is also licensed for both the treatment of psoriasis and IBD. We note that a significantly higher dose is necessary to achieve an adequate response for IBD symptoms.16,20

Expert opinion exists that methotrexate and cyclosporine are somewhat effective and can be used if necessary. Apremilast showed efficacy in a phase II study for ulcerative colitis.21

We recommend against the use of biological drugs: etanercept, secukinumab, ixekizumab and brodalumab, to treat psoriasis patients with active IBD, due to the risk of exacerbations of IBD with their use.22,23

Demyelinating diseases (MS/Guillain–Barré syndrome) Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system that affects approximately 1/1000 people in Belgium. The incidence and prevalence of psoriasis are higher in the MS population than in a matched cohort from the general population.24

Many of the available systemic biological and non-biological drugs may be used to treat psoriasis patients with demyelinating diseases such as MS or Guillain–Barré Syndrome, although supporting data are limited.

In psoriasis patients with demyelinating diseases such as MS, we recommend that the conventional drug dimethylfumarate is used as first-line therapy. This is because fumarates are indicated in psoriasis and in MS.24 We also recommend the IL12/23 inhibitor: ustekinumab due to data from the ACCEPT study supporting its use in psoriasis patients with concomitant MS.25

There is limited data supporting IL17 inhibitors: ixekizumab and secukinumab; there is some evidence to suggest that secukinumab may reduce MRI lesion activity in these patients.26 Acitretin may also be used as systemic treatment for psoriasis patients with MS or Guillain–Barré Syndrome.27,28 It is also our opinion that methotrexate is effective in the treatment of psoriasis patients with MS, but it is off-label in this indication.29,30

We advise colleagues not to use the anti-TNFα drug class, due to development of MS or worsening of pre-existing disease. We recommend against using adalimumab, certolizumab pegol, etanercept and infliximab in these patients. Discontinuation of the drug should be considered if any of these disorders develop or there is worsening of pre-existing disease.31–35 Indeed, there is evidence to suggest a higher risk of peripheral neuropathy in patients with rheumatic diseases who are past users of TNF-inhibitors.36

Chronic infections

Human immunodeficiency virus (HIV) HIV with undetectable viral load. It is a real challenge to manage already immunocompromised HIV+ patients with psoriasis. Most currently available systemic therapies for psoriasis are immunosuppressive, which poses a distinct clinical problem. We recommend that the opinion of infectious disease colleagues on the best approach to manage the already immunocompromised HIV+ patient with psoriasis is gained per case.

We recommend that either acitretin or apremilast is used first line in HIV+ patients. In our opinion, acitretin and apremilast are weak immunosuppressive drugs, and so the infection risk is not substantially increased with treatment.37,38

It is our opinion 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, can all be used as systemic treatments for HIV+ psoriasis with undetectable viral load undergoing highly active antiretroviral therapy (HAART). These agents may even have positive effects on CD4+ counts and viral load.39

We advise against using some of the conventional drugs including methotrexate, cyclosporine and fumarates in these patients, due to their immunosuppressive effect and potential adverse drug–drug interactions with HAART although these data are limited.40,41 Drug interactions should also be checked before starting apremilast, especially with CYP3A4 inducers.42

HIV with detectable viral load. We recommend gaining advise of infectious disease colleagues on the best approach to manage the already immunocompromised HIV+ patient with psoriasis.

From a safety perspective, we recommend using the non-biologicals, apremilast and acitretin, in HIV+ psoriasis patients with a detectable viral load. This is due to the good safety profile of these drugs on CD4+ T-lymphocyte count and HIV viral load in these patients.37,38 However, we also note that supporting data are limited. Other treatments should be case by case discussed with an infectious disease specialist. We discourage the use of methotrexate, cyclosporine and fumarates in HIV patients with detectable viral load.

Hepatitis C From a safety perspective, many of the biological drugs and some non-biological drugs available in Belgium (and listed below) can be used to treat those psoriasis patients who also have chronic hepatitis C infection, with minimal risk of viral reactivation. This advice is based on the European PSONET health insurance registry data.43

In psoriasis patients with chronic hepatitis C infection, it is our opinion that the following biological drugs, adalimumab and etanercept, are effective and well-tolerated short-term treatments in these patients. There are less data available supporting the use of infliximab and certolizumab pegol.44,45 There is also limited data supporting the use of the IL12/23 inhibitor ustekinumab, and the IL17 inhibitors secukinumab and
ixekizumab. Results from the first active comparator (ACCEPT) study of psoriasis biologic agents comparing ustekinumab and the TNF antagonist etanercept demonstrated that it is more appropriate to use etanercept rather than ustekinumab in psoriasis patients with hepatitis C infection.

We note a lack of data with the other IL23/p19 inhibitors: guselkumab, risankizumab and tildrakizumab; and the IL17 receptor blocker: brodalumab, and with the synthetic drug apremilast, in these patients.

We advise caution with the conventional drug, cyclosporine due to its strong immunosuppressive activity and reports of hepatotoxicity and liver injury with its use. Although these data are conflicting, we note that methotrexate is contra-indicated in these patients and so do not recommend its use in these patients. This advice is also extended to acitretin in these patients.

As there is potential risk of viral reactivation in psoriasis patients with chronic hepatitis C infection, we do recommend joint follow-up with hepatology colleagues together with close monitoring of liver tests and viral titres. A positive serology may suggest a risk of viral reactivation, and antiviral prophylaxis may be required. In most countries, hepatitis C treatment is present by the manufacturers. For the IL23/p19 inhibitors: guselkumab, risankizumab and tildrakizumab; the IL17 receptor blocker: brodalumab; the IL17 inhibitors: ixekizumab and secukinumab, no increased risk for TB reactivation has yet been reported.

We also note that TB testing is no longer mandatory from a scientific point of view (but is still present as a reimbursement criterion) for IL17 and IL23 antagonists, as well as with apremilast and acitretin. We note however that there are limited data available with the IL12/23 inhibitor: ustekinumab; the IL23/p19 inhibitors: guselkumab, risankizumab and tildrakizumab; the IL17 inhibitors: ixekizumab and secukinumab, may take several months to be eliminated before, during and after treatment with the systemic biological treatments. We advise that patients are monitored closely for TB infection and TB testing should be performed before, during and after treatment with the systemic biological drugs, as these drugs may take several months to be eliminated.

**Latent tuberculosis**. There is an increased risk of reactivation of latent TB infection with some immunosuppressant therapies. From a safety perspective, many of the biological and non-biological drugs available in Belgium to treat patients with psoriasis can be used to treat those patients who also have latent TB.

In psoriasis patients with latent TB, the IL17 inhibitors: ixekizumab and secukinumab; the IL23 inhibitors guselkumab, tildrakizumab and risankizumab as well as synthetic non-biological drugs, such as apremilast, and conventional drugs, such as acitretin and fumarates, may be used as systemic treatments. Caution is advised for methotrexate and cyclosporine. Given the critical role of TNF-α in granuloma formation, we advise also caution with use of the TNFα antagonists: adalimumab, certolizumab pegol, etanercept and infliximab as data suggest an increased risk of reactivation of latent TB infection with their use.

For the IL23/p19 inhibitors: guselkumab, risankizumab and tildrakizumab; the IL17 inhibitor: ustekinumab although cases of reactivation have been reported due to the inhibition of the critical IL-12 pathway in the regulation of immunity to *M. tuberculosis*. For the IL17 inhibitors: ixekizumab and secukinumab, no increased risk for TB reactivation has yet been reported.

Tuberculosis, including reactivation and new onset, has been reported in some patients receiving biological treatments. Therefore, we recommend that before initiation of biologicals of the anti-TNFα or anti-IL12/23 class or in case of anticipated long-term immunosuppressive treatment with conventional drugs, patients must be tested for both active and inactive (‘latent’) tuberculosis infection. If latent TB is diagnosed, appropriate treatment with anti-tuberculosis prophylaxis must be started before initiation of the treatment and continued for 1 month before starting the systemic psoriasis treatments. We advise that patients are monitored closely for TB infection before, during and after treatment with the systemic biological drugs, as these drugs may take several months to be eliminated (SmPCs).
Malignancies/cancer

Solid cancer Patients with psoriasis have a slight increase in the relative risk of developing solid organ malignancies, which increases with the severity of psoriasis. Therefore, careful consideration must be given to the systemic treatment of psoriasis patients with a history of a solid cancer.

From a safety perspective, we recommend that the following biological drugs, adalimumab, certolizumab pegol, etanercept, and infliximab and ustekinumab, as well as the following conventional drugs, methotrexate, fumarates and acitretin, and the synthetic drug apremilast, can be used as systemic treatments for psoriasis patients with a history of a solid cancer. We do advise that there is no need for waiting before commencing systemic treatment with acitretin, fumarates, methotrexate in psoriasis patients with a history of a solid cancer. However, we advise consulting with oncology colleagues before commencing treatment.

We recommend waiting 5 years before starting biological therapy in psoriasis patients with a history of a solid cancer in accordance with BAD guidelines. However, to the best of our knowledge there is no definitive evidence to demonstrate that these drugs, when used as monotherapy for the treatment of psoriasis, increase the risk of (recurrence of) malignancy. We therefore suggest that clinicians consult with oncology colleagues on a case-by-case basis, taking into consideration the stage, whether a cancer has been treated effectively and prognosis of the patient’s tumour before commencing treatment.

The conventional drug cyclosporine has tumour-promoting effects, and in the SmPC, a higher risk for lymphoma and other malignancies, especially skin malignancies, is mentioned. Therefore, it is also to be used with caution.

We advise caution with use of the synthetic drug apremilast, in psoriasis patients with a history of a solid cancer, due to insufficient long-term safety data being available although this drug has limited immunosuppressive properties. It is therefore less likely to impair antitumoral immunity.

We advise caution with the use of the anti-IL17 drugs, brodalumab, ixekizumab and secukinumab, and the anti-IL23 drugs, guselkumab, risankizumab and tildrakizumab, due to insufficient long-term safety data being available. Nonetheless, the IL23 and IL17 drugs are less likely to be involved in antitumoral immunity as they do not impair the Th1 response.

Haematological cancer Patients with psoriasis have a moderate increase in the relative risk of developing haematological malignancies, in particular, lymphoma, but the absolute risk

Table 1 Recommendations for the use of systemic psoriasis treatment according to (associated) inflammatory disorders

| Strong recommendation in favour | Weak recommendation in favour | Weak recommendation against | Strong recommendation against | Insufficient evidence to make a recommendation |
|--------------------------------|-------------------------------|-----------------------------|-----------------------------|----------------------------------|
| “Will likely be beneficial”    | “ Might be beneficial”         | “Will (likely) not help but cause no harm” | “ Likely to cause harm”       |                                  |
| Psoriasis arthritis            |                               |                             |                             |                                  |
| MTX                            | CYCLO*                        | ACIT*                       | FUM*                        |                                  |
| APR                            |                               |                             |                             |                                  |
| ADA, CERT, ETA, IFX, IXE, SECU, UST |                     |                             |                             |                                  |
| Inactive inflammatory bowel disease (IBD) |                       | ACIT*                       | ETE*                        |                                  |
| IFX, ADA, CERT*               | CYCLO*, MTX*, FUM*, APR*, GUS*, RIS*, TIL* |                             | ETE*, SEC*, IXE*, BROD* |                                  |
| UST                            |                               |                             |                             |                                  |
| Active inflammatory bowel disease (IBD) |                   | ACIT*                       | ETE*, SEC*, IXE*, BROD* |                                  |
| ADA, CERT*, IFX               | MTX*, CYCLO*                  |                             | FUM*, APR*, GUS*, RIS*, TIL* |                                  |
| UST                            |                               |                             |                             |                                  |
| Demyelinating diseases        | MTX*, IXE*, SECU*             | ACIT*                       | ADA*, CERT*, ETA*, IFX*      |                                  |
| FUM                            |                               |                             | CYCLO*, APR*, GUS*, RIS*, TIL*, BROD* |                                  |
| UST*                          |                               |                             |                             |                                  |

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.

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.
remains very low. Therefore, from a safety perspective we recommend that the following conventional systemic drugs, methotrexate, fumarates and acitretin, are used as first-line treatment of psoriasis patients with a history of haematological malignancies. We also advise that apremilast is often a good treatment option for these patients, based on our

| Strong recommendation in favour | Weak recommendation in favour | Weak recommendation against | Strong recommendation against | Insufficient evidence to make a recommendation |
|--------------------------------|-------------------------------|-----------------------------|-------------------------------|-----------------------------------------------|
| "Will likely be beneficial"    | "Will (likely) not help but likely cause no harm" | Evaluate case by case "Might or May harm" | "Likely to cause harm" | |
| HIV with undetectable viral load | ACIT, APR, ADA, CERT, ETA, IFX, UST, GUS, RIS, TIL, SEC, IXE, BROD | MTX, CYCLO, FUM | | |
| HIV with detectable viral load | ACIT, APR | MTX, CYCLO, FUM | ADA, CERT, ETA, IFX, UST, GUS, RIS, TIL, SEC, IXE, BROD | |
| Hepatitis C | APR, ADA, ETA, IFX, CERT, UST | CYCLO | ACIT, MTX | FUM, GUS, RIS, TIL, SEC, IXE, BROD |
| Hepatitis B | ACIT, CYCLO, APR, UST | IFX, ADA, ETA, CERT | MTX | FUM, GUS, RIS, TIL, SEC, IXE, BROD |
| Latent tuberculosis | ACIT, APR, FUM, IXE, SEC, BROD, GUS, RIS, TIL | CYCLO, MTX, UST | ADA, CERT, ETA, IFX | |
| Solid cancer | ACIT, MTX, CYCLO, FUM, APR, IFX, ADA, ETA, CERT*, UST* | | | GUS, RIS, TIL, SEC, IXE, BROD |
| Haematological cancer | MTX, FUM, ACIT, APR, UST* | | CYCLO, IFX, ADA, ETA, CERT, GUS, RIS, TIL, SEC, IXE, BROD | |
| Non-melanoma skin cancer (NMSC) | ACIT, FUM, APR, UST, GUS, RIS, TIL, BROD, IXE, SEC | MTX, CYCLO, IFX, ADA, CERT, ETA | | |
| Melanoma | ACIT, FUM, MTX | ADA*, IFX*, CERT*, ETA*, UST* | CYCLO | GUS, RIS, TIL, SEC, IXE, BROD, APR |

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.

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

*Wait for 5 year and/or consult oncology colleague.
clinical opinion, even though there is limited long-term (3 years now) safety data available.

For second-line treatment, we advise that the biological drug, ustekinumab, may be used. Insufficient data are present on the new IL-17 and IL-23 blockers.

We note that it is recommended to wait 5 years before commencing treatment with biological drugs in these patients. However, we advise consulting with onco-haematology colleagues before commencing treatment. The decision should be made on a case-by-case basis, taking into consideration the stage and prognosis of the patient’s tumour before commencing treatment.

**Skin cancer** Non-melanoma skin cancer. The risk of non-melanoma skin cancer (NMSC) increases with age and severity of psoriasis, although contradictory findings exist. From a safety perspective, we also recommend that the biological IL12/23 inhibitor, ustekinumab, may be used in the systemic treatment of psoriasis patients with a history of non-melanoma skin cancers.

We also advise that the synthetic drug apremilast can be used in these patients as no safety signal has yet been identified. Nonetheless, data are limited.

For the more clinically important cutaneous squamous cell carcinoma (SCC), we advise that the anti-TNFα biological drugs, adalimumab, certolizumab pegol, etanercept and infliximab and the conventional drugs methotrexate and cyclosporine, are contra-indicated in psoriasis patients with aggressive or invasive SCC. This is because the risk of SCC is increased in psoriasis and an increased risk has also been reported with these drugs. However, we note that well-differentiated and in situ lesions do not constitute a contraindication, and these drugs are not contra-indicated in psoriasis patients with a history of basal cell carcinoma (BCC). There is no contraindication for patients with BCC although an alternative therapy can be considered.

We advise caution with the newer anti-IL17 drugs, ixekizumab, secukinumab and IL-17 receptor blocker brodalumab and the IL23 inhibitors, guselkumab, risankizumab and tildrakizumab due to insufficient clinical follow-up data. However, as these newer drugs do not target the Th1 pathway and IL-17 has currently no theoretical ground suggesting an increased risk of skin cancer with these treatments.

However, we wish to emphasize that reduction in common risk factors such as sun exposure or phototherapy (in particular PUVA) has a much greater effect on reducing cancer burden in patients with psoriasis than stopping or avoiding systemic immune modulatory agents.

---

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

| Condition                  | ACITR | CYCLO | MTX | FUM | APR | IFX | ETA | ADA | CERT | USTE | GUS | RIS | TIL | SECU | IXE | BROD |
|----------------------------|-------|-------|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|------|-----|-------|
| PsA peripheral             | B     | A     | A   | C   | A   | A   | A   | A   | A    | B    | A   | A   | A   | A    | A    |       |
| PsA spine                  | B     | A     | A   | NA  | A   | A   | A   | A   | A    | A    | NA  | A   | A   |       |       |       |
| PsA enthesitis/dactylitis  | B     | A     | A   | NA  | A   | A   | A   | A   | A    | A    | A   | A   | A   |       |       |       |
| Inactive IBD               | C     | C     | A   | NA  | C   | A   | A   | A   | A    | C    | C   | C   | C   |       |       |       |
| Active IBD                 | C     | C     | A   | NA  | C   | A   | A   | A   | A    | C    | A   | A   | A   |       |       |       |
| HIV active                 | B     | C     | C   | C   | C   | C   | C   | C   | C    | C    | C   | C   | C   |       |       |       |
| HIV non-active             | B     | B     | B   | A   | B   | B   | B   | B   | B    | B    | B   | B   | B   |       |       |       |
| Chronic Hep C              | C     | B     | B   | C   | C   | B   | B   | B   | B    | C    | C   | C   | C   |       |       |       |
| Chronic Hep B              | B     | B     | A   | NA  | B   | B   | B   | B   | B    | NA   | NA  | NA  | B   | C    | C    |       |
| Latent TB                  | B     | C     | C   | NA  | A   | A   | A   | A   | A    | C    | C   | C   | C   | C    | C    |       |
| Demyelinating disease      | C     | B     | B   | A   | NA  | A   | A   | A   | A    | A    | NA  | NA  | NA  | C    | NA   | NA   |
| Cancer                     | C     | A     | B   | NA  | C   | B   | B   | B   | B    | NA   | NA  | NA  | NA  | NA   | NA   |       |

Levels of evidence: A (high level of evidence: randomized clinical trials, extensive experience in clinical practice), B (moderate level of evidence: observational studies, limited randomized clinical trials, moderate experience in clinical practice), C (very low level of evidence: case series, retrospective without controls, low experience in clinical practice).

Results of the studies: (i) Green: preserved efficacy without increased adverse events or worsening of the comorbidity; (ii) Yellow: limited risk of decreased efficacy and/or limited risk of increased adverse events or worsening of the comorbidity; (iii) Orange: moderate risk of decreased efficacy and/or moderate risk of increased adverse events or worsening of the comorbidity; (iv) 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.
Melanoma. Interestingly, the risk for melanoma in patients with psoriasis may be lower than in individuals without psoriasis.66 In psoriasis patients with a history of melanoma, we recommend using the conventional drugs, acitretin, fumarates and methotrexate, as systemic therapy.78–81

When using the anti-TNFα drugs, adalimumab, certolizumab pegol, etanercept and infliximab, and the IL-12/23 inhibitor, ustekinumab, we note that the BAD guidelines recommend waiting for 5 years before starting these biological therapies in psoriasis patients with a history of melanomas.82 Exposure to TNFα inhibitors has been linked to an increased development of melanoma, and cases with metastatic melanoma under TNFα inhibitors have been reported.82–84 To date, an increased risk for melanoma has not been confirmed for ustekinumab.85 Data for other IL-23 inhibitors, IL-17 inhibitors or IL-17 receptor blocker are limited.86 The recurrence of melanoma has been described in one patient receiving apremilast.87

We suggest that clinicians consult with oncology colleagues on a case-by-case basis and take into consideration the stage and prognosis of the patient’s tumour.

Discussion
Creating practice guidelines (BETA-PSO) to treat psoriasis patients with comorbidities is complex as new treatments are being introduced which have limited available data in subgroups of patients with specific comorbidities. The evidence used to make our recommendations is summarized in Tables 1, 2 and 3.

Fortunately, most psoriasis drugs have a well-documented efficacy in psoriatic arthritis.

The obvious caveats are to prescribe TNF-α blockers in patients with tuberculosis and multiple sclerosis or IL-17 blockers in patients with inflammatory bowel disease. Practising dermatologists should be encouraged to gather a thorough medical history which includes the family medical history (e.g. relatives with IBD). In patients with cancer or hepatitis/HIV infection, broad immunosuppressants and targeted treatments affecting the Th1 response should be avoided. An exception seems to be ustekinumab which despite its IL-12 inhibiting capacity carries only a relative contraindication in non-active HIV infection and cancer.85

Anti-IL17 blockers and receptor blockers, anti-IL23 antibodies and acitretin are in theory believed to exhibit no to very limited impairment of antiviral and antitumoral responses although more long-term data are needed.88 Studies on fumarates are for several comorbidities limited or lacking. Apremilast seems to have limited immunosuppressive properties and is considered a safe option in most high-risk patients although its efficacy in psoriasis is less impressive compared to the newest biologics.

We believe this BETA-PSO project offers a valuable contribution facilitating a well-informed decision to initiate systemic treatment in complex psoriasis patients. 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.

Acknowledgements
We wish to thank the other board members of the Royal Belgian Society of Dermatology and Venerology: Josette André, Bernard Bouffioux, Véronique del Marmol, Marjan Garmyn, Jan Gutermuth, Stéphanie Ryckaert, Marc Vandaele and Katrien Vossaert, for their advice in the design and their continuous support of this work.

References
1 Zachariae H. Prevalence of joint disease in patients with psoriasis: implications for therapy. Am J Clin Dermatol 2003; 4: 441–447.
2 Fu Y, Lee C-H, Chi C-C. Association of psoriasis with inflammatory bowel disease: a systematic review and meta-analysis. JAMA Dermatol 2018; 154: 1417–1423.
3 Ma C, Panaccione R, Khanna R, Feagan BG, Jairath V. IL-12/23 or selective IL-23 inhibition for the management of moderate-to-severe Crohn’s disease? Best Pract Res Clin Gastroenterol 2019; 38–39: 101604.
4 Hueber W, Sands BE, Lewitzky S et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn’s disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut 2012; 61: 1693–1700.
5 Hohenberger M, Cardwell LA, Oussedik E, Feldman SR. Interleukin-17 inhibition: role in psoriasis and inflammatory bowel disease. J Dermatol Treat 2018; 29: 13–18.
6 Emmond B, Ellis LA, Chakravarty SD, Ladouceur M, Lefebvre P. Real-world incidence of inflammatory bowel disease among patients with other chronic inflammatory diseases treated with interleukin-17a or phosphodiesterase 4 inhibitors. Curr Med Res Opin 2019; 35: 1751–1759.
7 Silfvest-Kaiser AS, Homan KB, Hansouri B. A narrative review of psoriasis and multiple sclerosis: links and risks. Psoriasis (Auckl) 2019; 9: 81–90.
8 Trafford AM, Parisi R, Kontopantelis E, Griffiths CEM, Ashcroft DM. Association of psoriasis with the risk of developing or dying of cancer: a systematic review and meta-analysis. JAMA Dermatol 2019; 155: 1390.
9 Geller S, Xu H, Lebwohl M, Nardone B, Lacouture ME, Ketherpal M. Malignancy risk and recurrence with psoriasis and its treatments: a concise update. Am J Clin Dermatol 2018; 19: 363–375.
10 Singh JA, Guyatt G, Oudiea A et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Rheumatol 2019; 71: 5–32.
11 Sakkas LI, Zafiriou E, Bogdanos DP. Mini review: new treatments in psoriatic arthritis. Focus on the IL-23/17 axis. Front Pharmacol 2019; 10: 872.
12 Oh EH, Koh WS, Shin JM, Kim JE, Ko JY, Ro YS. Clinical experience of cyclosporin treatment in patients with psoriasis and psoriatic arthritis. J Dermatol Treat 2018; 45: 329–330.
13 Olivieri I, Salvareni C, Cantini F et al. Therapy with cyclosporine in psoriatic arthritis. Semin Arthritis Rheum 1997; 27: 36–43.
14 Peeters AJ, Dijkmans BA, Van der Schorff JG. Fumaric acid therapy for psoriatic arthritis. Best Pract Res Clin Rheumatol 2019; 504.
15 Whitlock SM, Enos CW, Armstrong AW et al. Management of psoriasis in patients with inflammatory bowel disease: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2018; 78: 383–394.
16 Wong U, Cross RK. Expert opinion on interleukin-12/23 and interleukin-23 antagonists as potential therapeutic options for the treatment of inflammatory bowel disease. Expert Opin Investig Drugs 2019; 28: 473–479.
34 Cimzia 200 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/3831/smpc#POSOLOGY (last accessed: 25 January 2020).
35 Remicade 100mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/3831/smpc#POSOLOGY (last accessed: 25 January 2020).

17 Suleiman AA, Khatri A, Minocha M, Othman AA. Population phar- macokinetics of the interleukin-23 inhibitor risankizumab in subjects with psoriasis and Crohn’s disease: analyses of phase I and II trials. *Clin Pharmacokinet* 2019; 58: 375–387.
18 Iriarte A, Zaera C, Bachiller-Corral J, López-Sanromán A. Inflammatory bowel disease as a paradoxical effect of anti-TNF alpha therapy. *Gastroenterol Hepatol* 2017; 40: 117–121.
19 Knayzev OV, Kragamanova AV, Lishchinskaya AA et al. Efficacy and tolerability of certolizumab pegol in Crohn’s disease in clinical practice. *Ter Arkh* 2018; 90: 74–80.
20 Ahmed Z, Venkata K, Zhang N, Malik TA. Comparative effectiveness of ustekinumab versus adalimumab in induction of clinical response and remission in Crohn’s disease: experience of a real-world cohort at a tertiary care inflammatory bowel disease referral center. *Gastroenterology Res* 2019; 12: 245–251.
21 Danese S, Neurath MF, Kopon A et al. Effects of apremilast, an oral inhibitor of phosphodiesterase 4, in a randomized trial of patients with active ulcerative colitis. *Clin Gastroenterol Hepatol* 2020; 18. https://doi.org/10.1016/j.chg.2019.12.032.
22 Korzenik J, Larsen MD, Nielsen J, Kjeldsen J, Norgård BM. Increased risk of developing Crohn’s disease or ulcerative colitis in 17 018 patients under treatment with anti-TNF-α agents, particularly etanercept, for autoimmune diseases other than inflammatory bowel disease. *Aliment Pharmacol Ther* 2019; 50: 289–294.
23 Targan SR, Feagan B, Vermeire S et al. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn’s disease. *Am J Gastroenterol* 2016; 111: 1599–1607.
24 Marrie RA, Patten SB, Tremlett H, Wolfson C, Leung S, Fisk JD. Increased incidence and prevalence of psoriasis in multiple sclerosis. *Mult Scler Relat Disord* 2017; 13: 81–86.
25 Segal BM, Constantinescu CS, Raychaudhuri A et al. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. *Lancet Neurol* 2008; 7: 807–804.
26 Havrdová E, Belova A, Goloborodko A et al. Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomised, proof-of-concept study. *J Neurol* 2016; 263: 1287–1295.
27 Venturini M, Zanca A, Venturuzzo A et al. Secukinumab for patients with plaque psoriasis affected by multiple sclerosis: a mini-review with a representative case report. *J Eur Acad Dermatol Venereol* 2020; 34: e110–e112.
28 Macaluso F, Guggino G, Mauro D, Rizzo C, Bignone R, Ciccia F. Safety and efficacy of secukinumab treatment in a patient with ankylosing spondylitis and concomitant multiple sclerosis. *Clin Exp Rheumatol* 2019; 37: 1096.
29 Gray O, McDonnell GV, Forbes RB. Methotrexate for multiple sclerosis. *Cochrane Database Syst Rev* 2004; CD003208.
30 Ashrati F, Savej MR. Effects of low dose methotrexate on relapsing-remitting multiple sclerosis in comparison to Interferon-β-1a: a randomized controlled trial. *J Res Med Sci* 2011; 16: 457–462.
31 Honda Y, Otsuka A, Egawa G et al. Multiple neurological abnormalities, including pontine hemorrhage, multiple sclerosis and aseptic meningitis, during anti-TNF-α therapy in psoriatic arthritis. *Eur J Derma- tol* 2015; 25: 487–488.
32 Humira 40 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/2150/smpc (last accessed: 25 January 2020).
33 Embrel 25 mg powder and solvent for solution for injection - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/3837/smpc (last accessed: 25 January 2020).
34 Cimzia 200 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/4450/smpc (last accessed: 25 January 2020).
35 Remicade 100mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/3831/smpc#POSOLOGY (last accessed: 25 January 2020).
36 Etminan M, Sodhi M, Samii A, Carleton BC, Kezouh A, Antonio Avina-Zubieta J. Tumor necrosis factor inhibitors and risk of peripheral neuropathy in patients with rheumatic diseases. *Semin Arthritis Rheum* 2019; 48: 1083–1086.
37 Reddy SP, Shah VV, Wu JJ. Apremilast for a psoriasis patient with HIV and hepatitis C. *J Eur Acad Dermatol Venereol* 2017; 31: e481–e482.
38 Lee CS, Li K. A review of acitretin for the treatment of psoriasis. *Expert Opin Drug Saf* 2009; 8: 769–779.
39 Nakamura M, Abrouk M, Farahnik B, Zhu TH, Bhutani T. Psoriasis treatment in HIV-positive patients: a systematic review of systemic immunosuppressive therapies. *Caitis* 2018; 101: 38; 42; 56.
40 Methotrexate 2.5 mg Tablets - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/511/smpc (last accessed: 25 January 2020).
41 Neoral Soft Gelatin Capsules - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/1034/smpc (last accessed: 25 January 2020).
42 Nast A, Spuls PI, van der Kraaij G et al. European S3-guideline on the systemic treatment of psoriasis vulgaris - update apremilast and secukinumab - EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2017; 31: 1951–1963.
43 Couderc S, Lapeyre-Mestre M, Bourrel R, Paul C, Montaстрuc J-L, Sommet A. Infectious risk of biological drugs vs. traditional systemic treatments in moderate-to-severe psoriasis: a cohort analysis in the French insurance database. *Fundam Clin Pharmacol* 2018; 32: 436–449.
44 Velázquez Tarjuelo D, de la Cueva Dobao P. Certolizumab in a patient with severe psoriasis and concomitant hepatitis C virus infection. *JADACase Rep* 2018; 4: 833–834.
45 Oniankian O, Duvoix C, Challine D et al. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol* 2004; 31: 107–109.
46 Piaierico S, Messina F, Russo FP. Managing psoriasis in patients with HIV or HCV infection: practical considerations. *Am J Clin Dermatol* 2017; 20: 829–845.
47 Galluzzo M, D’Adamo S, Silvaggio D et al. Ustekinumab treatment for moderate-to-severe plaque psoriasis: eight-year real-life experience. *Expert Opin Biol Ther* 2020; 20: 95–104.
48 Young MS, Horn EJ, Cather JC. The ACCEPT study: ustekinumab versus etanercept in moderate-to-severe psoriasis patients. *Expert Rev Clin Immunol* 2011; 7: 9–13.
49 Klinktmalm GBG, Iwatsuki S, Starzl TE. Cyclosporin A hepatotoxicity in 66 renal allograft recipients. *Transplantation* 1981; 32: 488–489.
50 Kaushik SB, Lebwohl MG. Psoriasis: which therapy for which patient: psoriasis comorbidities and preferred systemic agents. *J Am Acad Derma- tol* 2019; 80: 27–40.
51 Acitretin 25mg Capsules - Summary of Product Characteristics (SmPC) - (emc). URL https://www.medicines.org.uk/emc/product/5264/smpc (last accessed: 25 January 2020).
52 Chiuy H-Y, Hui RC-Y, Huang Y-H et al. Safety profile of secukinumab in treatment of patients with psoriasis and concurrent hepatitis B or C: a multicentric prospective cohort study. *Acta Derm Venereol* 2018; 98: 829–834.
53 Crowley J, Thà¢ D, Joly P et al. Long-term safety and tolerability of apremilast in patients with psoriasis; pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol* 2017; 37: 310–317.e1.
54 Bonifaci C, Lora V, Graceffa D, Nosotti L. Management of psoriasis patients with hepatitis B or hepatitis C virus infection. *World J Gastroenterol* 2016; 22: 6444–6455.
