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)

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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.

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Conflicts of interest

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

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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.[3] In contrast, IL-17 blockade is ineffective in Crohn's disease and may cause disease exacerbations.[4,5] 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.[7] 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.[9] 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-biologic 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.[10] 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.[11]

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.[12,13] 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.[14] 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 IL23/p19 inhibitors: guselkumab, 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.[15–17]

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.[6] We also advise not using etanercept in these patients due to the possibility of a flare-up of IBD symptoms.[18]

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.[15] We

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-biologics, 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.[46,47] 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.[48]

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.[48]

We advise caution with the conventional drug, cyclosporine due to its strong immunosuppressive activity and reports of hepatotoxicity and liver injury with its use.[49] 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.[40,50,51]

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.[52] In most countries, hepatitis C treatment is present and leads to full eradication. In that case, no further follow-up is needed.

Hepatitis B Similar to those patients with hepatitis C co-infection, from a safety perspective, most of the biological drugs and some non-biological drugs available in Belgium can be used with caution to treat psoriasis patients who also have chronic hepatitis B infection, with minimal risk of viral reactivation.

In psoriasis patients with chronic hepatitis B infection, it is our opinion that the biological drug ustekinumab and the conventional drugs, acitretin and cyclosporine as well as apremilast can be used with caution as systemic psoriasis therapy – in terms of hepatitis B infection risk. Data from two large clinical trials also show that the risk of hepatitis B infection is similar with or without apremilast treatment.[46,53] The only reports from reactivation of hepatitis B with cyclosporin are from severe immunosuppressed patients.[54] Reactivation of hepatitis B occurred in 39% of HBsAg+ patients treated with TFN-α-blockers for autoimmune diseases but not in HBsAg-/anti-HBc+ patients.[55]

We note that methotrexate is contra-indicated in these patients, due to significant risk of reactivation of hepatitis B with a potentially fatal outcome and so advise against its use.[40] Some studies have also shown that the systemic biologics such as TNF antagonists may cause reactivation of hepatitis B and also with anti-IL17, secukinumab, treatment.[50,52,56] We therefore advise that psoriasis patients who are HBV carriers are closely monitored for hepatitis B reactivation. If hepatitis B reactivation occurs, then antiviral prophylaxis should be given concomitantly in consultation with infectious disease colleagues and as advised by the manufacturers.

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.[57] This risk seems less so with the IL12/23 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*.[58–60]

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.[61–64]

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 receptor blocker: brodalumab in these patients.

There are now some data available to suggest that the IL17 inhibitors (secukinumab and ixekizumab) may be better tolerated regarding latent TB reactivation risk compared with the TNFα and IL-12/23 antagonists in psoriasis patients with TB.[62] Likewise, there are also some data to suggest that etanercept may be a better treatment option than adalimumab in these patients, although the evidence is limited.[65]

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.[66] 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.[9] 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.[67] 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.[41,68] 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.[69,70] 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 *"Will likely be beneficial"*	Weak recommendation in favour *"Might be beneficial"*	Weak recommendation against *"Will (likely) not help but cause no harm"*	Strong recommendation against *"Likely to cause harm"*	Insufficient evidence to make a recommendation
Psoriasis arthritis				
MTX APR ADA, CERT, ETA, IFX IXE, SECU, UST	CYCLO* BROD* GUS*, RIS*, TIL*	ACIT* FUM*		
Inactive inflammatory bowel disease (IBD)				
IFX, ADA, CERT* UST	CYCLO*, MTX*, FUM* APR* GUS*, RIS*, TIL*	ACIT*	ETA* SEC*, IXE*, BROD*	
Active inflammatory bowel disease (IBD)				
ADA, CERT*, IFX UST	MTX*, CYCLO*	ACIT*	ETA* SEC*, IXE*, BROD*	FUM* APR* GUS*, RIS*, TIL*
Demyelinating diseases				
FUM UST*	MTX* IXE*, SECU*	ACIT*	ADA*, CERT*, ETA*, IFX*	CYCLO* APR GUS*, RIS*, TIL* BROD*

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.[66] 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

Table 2 Recommendations for the use of systemic psoriasis treatment according to coexisting infectious or malignant disorders

Strong recommendation in favour *"Will likely be beneficial"*	Weak recommendation in favour *"Will (likely) not help but likely cause no harm"*	Weak recommendation against Evaluate case by case *"Might or May harm"*	Strong recommendation against *"Likely to cause harm"*	Insufficient evidence to make a recommendation
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, CYLO 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; IXE, 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.[67] 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.[71,72] From a safety perspective for those psoriasis patients with a history of skin cancer, we advise the conventional drugs, methotrexate, fumarates and acitretin, may be used as systemic treatment. Since acitretin is likely to be protective against a variety of solid and haematological malignancies, including cutaneous squamous cell carcinoma, we advise that acitretin can be used in combination with these other systemic drugs and at a lower dose according to the therapeutic result.[73–75] 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.[76] 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 been shown to induce skin cancer cell proliferation there is currently no theoretical ground suggesting an increased risk of skin cancer with these treatments.[77]

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.[66]

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

	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	A	A	A	B	A	A	A
PsA spine	B	A	A	NA	A	A	A	A	A	A	A	A	NA	A	A	A
PsA enthesitis/dactylitis	B	A	A	NA	A	A	A	A	A	A	A	A	B	A	A	A
Inactive IBD	C	C	A	C	C	A	C	A	A	A	C	A	C	C	C	C
Active IBD	C	C	A	NA	C	A	A	A	A	A	C	A	C	A	A	A
HIV active	B	C	C	C	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	B	B	B
Chronic Hep C	C	B	B	C	C	B	B	B	B	C	C	C	C	C	C	C
Chronic Hep B	B	B	A	NA	B	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	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	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.[67] Exposure to TNFα inhibitors has been linked to an increased development of melanoma, and cases with metastatic melanoma under TNFα inhibition 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 psoriasis 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.

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