Psoriasis: Which therapy for which patient

Psoriasis comorbidities and preferred systemic agents

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Learning objectives
After completing this learning activity, participants should be able to describe briefly the evidence-based therapeutic options available to treat psoriasis and discuss emerging therapies and review their safety, efficacy, and impact on overall disease burden of psoriasis.

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Psoriasis is a systemic inflammatory disease associated with increased risk of comorbidities, such as psoriatic arthritis, Crohn's disease, malignancy, obesity, and cardiovascular diseases. These factors have a significant impact on the decision to use one therapy over another. The past decade has seen a paradigm shift in our understanding of the pathogenesis of psoriasis that has led to identification of new therapeutic targets. Several new drugs have gained approval by the US Food and Drug Administration, expanding the psoriasis armamentarium, but still a large number of patients continue to be untreated or undertreated. Treatment regimens for psoriasis patients should be tailored to meet the specific needs based on disease severity, the impact on quality of life, the response to previous therapies, and the presence of comorbidities. The first article in this continuing medical education series focuses on specific comorbidities and provides insights to choose appropriate systemic treatment in patients with moderate to severe psoriasis. (J Am Acad Dermatol 2019;80:27-40.)

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Abbreviations used:

ATIL:	anti–tumor necrosis factor-α–induced lupus
CD:	Crohn's disease
CHF:	congestive heart failure
DLE:	discoid lupus erythematosus
IBD:	inflammatory bowel disease
LE:	lupus erythematosus
MACE:	major adverse cardiovascular event
MI:	myocardial infarction
MS:	multiple sclerosis
NMSC:	nonmelanoma skin cancer
NYHA:	New York Heart Association
OLE:	open label extension
PASI:	Psoriasis Area Severity Index
RCT:	randomized controlled trial
SCC:	squamous cell carcinoma
SCLE:	subacute cutaneous lupus erythematosus
UC:	ulcerative colitis

Psoriasis is a systemic inflammatory disease that is associated with an increased risk of comorbidities, such as hypertension, hyperlipidemia, major adverse cardiovascular events (MACEs), inflammatory arthritis, malignancy, obesity, and inflammatory bowel disease (IBD).[1] These comorbidities often impact the decision to use one therapy over another, and it is important to keep the individual patient characteristics in mind while choosing a treatment regimen for patients with psoriasis. The past decade has witnessed a paradigm shift in our understanding of psoriasis pathophysiology that has led to the identification of multiple new therapeutic targets. Whereas older treatment modalities, such as phototherapy, are still effective, not every patient can attend frequent phototherapy treatments or has access to home phototherapy units. This continuing medical education series is therefore focused on systemic treatments. Studies have shown that many physicians lack confidence in prescribing systemic drugs, especially biologics, and therefore tend to follow a one size fits all approach that often leads to inadequate results and poor patient satisfaction.[2] Treatment regimens for patients with psoriasis should be tailored to meet their specific needs based on disease severity, the impact on quality of life, response to previous therapies, and the presence of comorbidities. This 2-part continuing medical education series focuses on specific comorbidities and provides insights for choosing an appropriate systemic treatment for patients with psoriasis.

PSORIATIC ARTHRITIS

Psoriatic arthritis develops in ≤30% of patients, but severe deforming arthritis is much less common, seen in about 5% patients. Psoriasis usually precedes joint manifestations in ≤85% patients by 10 years on average; however, in approximately 15% of cases, arthritis either precedes or occurs simultaneously with skin disease.[3-6] There is a paucity of validated tools for the assessment of drug efficacy in patients with psoriatic arthritis; therefore, American College of Rheumatology (ACR) criteria for rheumatoid arthritis are used to grade psoriatic arthritis improvement in clinical trials. Most clinical trials assessing psoriatic arthritis use the Sharp–van der Heijde modified method to score and document radiographic changes in patients with psoriatic arthritis.

Traditional agents

Methotrexate decreases inflammation in psoriatic arthritis but does not inhibit radiographic progression of disease. Other than the Tight Control of Psoriatic Arthritis study, there are few data confirming the efficacy of methotrexate in psoriatic arthritis.[7-9] Studies have shown cyclosporine to be beneficial in reducing peripheral (but not axial) joint involvement in patients with psoriatic arthritis.[10-14] Cyclosporine leads to better joint disease control when used with methotrexate and etanercept.[15,16] Acitretin has modest efficacy for psoriatic arthritis and is almost never used alone for its management.

Biologics and other newer agents

Tumor necrosis factor-α (TNF-α) inhibitors have a significant impact on the clinical symptoms of psoriatic arthritis and inhibit progressive structural damage of joints.[17,18] Mease et al[10] explored the efficacy and safety of etanercept and reported significant improvement in all study measures (ACR, Psoriasis Area and Severity Index [PASI], 36-item short form survey, health assessment questionnaire, etc) at 12 weeks. Subsequently, infliximab, adalimumab, golimumab, and certolizumab showed similar degrees of effectiveness and are now approved for patients with psoriatic arthritis.[19-22] Phase 3 trials of ustekinumab for psoriatic arthritis demonstrated significant improvement in joint disease and slower radiographic progression compared with placebo.[22] However, data suggest that TNF-α inhibitors are more effective in treating psoriatic arthritis than ustekinumab.[10,23-25] Bonifati and Graceffa[26] reported 7 patients who experienced worsening or a flare of psoriatic arthritis after they were switched from TNF-α inhibitors to ustekinumab, suggesting that ustekinumab has better performance on skin symptoms than on joint inflammation.

Phase 3 trials for secukinumab demonstrated the efficacy of secukinumab in the key end points of psoriatic arthritis, including slowing radiographic progression of the disease.[27-29] Generally, higher

ACR responses were noted in the anti—TNF-α naive populations and efficacy was sustained through week 52.[28] Similarly, phase 3 studies of ixekizumab demonstrated significant improvement in psoriatic arthritis disease activity and structural progression in biologic-naive patients.[30,31] Preliminary trials for brodalumab and psoriatic arthritis show good results but final data are lacking.[27,32] In the PALACE trials for apremilast, significantly more patients achieved ACR20 (ie, an improvement of 20% in the number of tender and number of swollen joints and a 20% improvement in 3 of the following 5 criteria: patient global assessment, physician global assessment, functional ability measure, visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein) response at week 16 compared with placebo regardless of previous treatment. Sustained improvements were seen through week 52 in the PALACE 1, 2, and 3 studies.[22,33-35] Studies have suggested a lack of efficacy of apremilast in axial disease.[36]

IL-23 inhibitors have been approved for the treatment of psoriasis, but studies assessing their effect on psoriatic arthritis are still underway. Abatacept was recently approved for use in psoriatic arthritis. A phase 2 study of 170 psoriatic arthritis patients demonstrated significant improvement of ACR20 response. A magnetic resonance imaging study of hands or feet at 24 weeks demonstrated improved synovitis, erosion, and osteitis scores. Skin psoriasis responses were modest.[37]

Expert opinion

1. Currently, 5 TNF-α inhibitors (etanercept, infliximab, adalimumab, certolizumab, and golimumab), 2 interleukin-17 (IL-17) blockers (secukinumab and ixekizumab), methotrexate, apremilast, tofacitinib, and abatacept are approved by the US Food and Drug Administration for the treatment of psoriatic arthritis.
2. While ustekinumab demonstrates good efficacy in psoriatic arthritis, its impact on skin disease is much more impressive than on joint disease.
3. Apremilast is effective in treating psoriatic arthritis, but prevention of radiologic progression has not been demonstrated.
4. Novel IL-23 inhibitors are currently under investigation for the treatment of psoriatic arthritis.
5. Methotrexate improves symptoms of joint disease but does not alter radiographic progression of disease.
6. Cyclosporine and acitretin have modest efficacy but are almost never used as monotherapy for psoriatic arthritis.

CROHN'S DISEASE

Psoriasis and Crohn's disease (CD) are chronic inflammatory disorders with similarities in genetic susceptibilities and immune-mediated inflammation.[38-40] Several studies have reported a high rate of co-occurrence of psoriasis and IBD.[41-46]

Traditional agents

A 2012 Cochrane review suggested that parenteral methotrexate (intramuscularly 25 mg/week) is more efficacious than placebo in inducing and maintaining remission in CD but is not as effective at lower doses.[47] Cyclosporine has proven to induce remission in patients with refractory CD.[48,49] There are no direct studies on acitretin use in CD. However, there are a few case reports that associate isotretinoin with development of IBD. Contrarily, a metaanalysis reported that isotretinoin use does not increase the risk of IBD. Despite any proven association, there have been multiple litigations associating isotretinoin to the development of IBD.[50-52]

Biologics and other newer agents

Infliximab, adalimumab, and certolizumab are approved by the US Food and Drug Administration for the treatment of CD. Anti—TNF-α agents are considered first-line management of moderate to severe CD, except for etanercept; in contrast, etanercept does not exhibit the same efficacy as other agents, likely because of its distinct pharmacodynamics.

Two landmark studies (ACCENT-I/ACCENT-II) proved the efficacy and guide the current use of infliximab in CD.[53,54] Efficacy of adalimumab in inducing and maintaining remission was demonstrated in the Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in CD and Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance trials in infliximab naïve and exposed patients, respectively.[55] In addition, pivotal phase 3 trials of adalimumab (PRECISE, WELCOME) demonstrated its efficacy in patients with CD, including those who failed infliximab therapy.[56,57] Indirect evidence suggests that there is no significant difference in efficacy between infliximab and adalimumab, whereas certolizumab may be less effective in inducing remission in patients with CD.[58,59] Golimumab is approved by the US Food and Drug Administration for the treatment of ulcerative colitis (UC), but additional studies are needed to assess its efficacy in CD.[60] Based on pivotal phase 3 trials (UNIT-1, UNIT-2 and IM-UNIT1), ustekinumab was approved for the treatment of CD in 2016.[61] IL-17 inhibitors have been linked to either induction or

exacerbation of preexisting CD. Clinical trials for secukinumab revealed incidence rates of 0.11 per 100 patient-years for CD.[62] Another study by Hueber et al[63] reported no clinical benefit of secukinumab in patients with moderate to severe CD. A pooled analysis of ixekizumab phase 3 studies for psoriasis reported results comparable to secukinumab with small numbers of CD cases reported.[64] An adjudication analysis performed by Reich et al[65] suggested that flare ups and new CD cases during ixekizumab exposure were uncommon (<1%).[65] Clinical trials for brodalumab reported 1 case of CD.[66,67] According to the Centers for Disease Control and Prevention, the estimated prevalence of IBD (including CD and UC) is 1.3% in the United States, and the data suggest that the rate of CD in patients treated with IL-17 inhibitors is about the same as would be expected. Among the IL-23 inhibitors, risankizumab was noted to be superior to placebo in achieving clinical remission in patients with moderate to severe refractory CD.[68] Phosphodiesterase type 4 inhibition has shown beneficial effects in animal models of colitis, but more human data are awaited.[69,70] CD flare has not been reported with apremilast but it causes diarrhea as a side effect.

Expert opinion

1. Infliximab, adalimumab, certolizumab, and ustekinumab are approved for the treatment of patients with CD. Golimumab is approved for UC but not for CD.
2. Etanercept is not as effective as other TNF-α inhibitors for CD.
3. A direct causal relationship between IL-17 inhibitors and CD has not been established but some clinicians avoid them in patients with a diagnosis or history suggestive of IBD.
4. IL-23 inhibitor use in CD has promising results in preliminary studies, but more data are needed to draw definite conclusions.
5. Methotrexate and cyclosporine can be used. There is no proven association between retinoids and CD, but some clinicians avoid acitretin in patients with a diagnosis or history suggestive of IBD.

MALIGNANCY

Traditional agents

The association of methotrexate with malignancies is not clear in patients with psoriasis. In a long-term study of 248 psoriasis patients treated with methotrexate, 10 patients developed malignant neoplasms including lymphomas, but this study concluded that methotrexate therapy for psoriasis did not contribute to the development of neoplasms.[71] However, there are several reports of newly diagnosed Epstein–Barr virus–associated lymphomas in patients with psoriasis who were taking methotrexate.[72-75] Long-term high-dose cyclosporine is associated with solid organ, skin, and lymphoproliferative cancers in transplant recipients. Cyclosporine increased the overall incidence of malignancy 2-fold (a 6-fold increase in squamous cell carcinoma [SCC]) in 1252 psoriasis patients after an average of 1.9 years of treatment. Previous exposure to psoralen plus ultraviolet A light phototherapy, methotrexate, or other immunosuppressive therapy was a significant risk factor.[76] Systemic retinoids prevent or delay the development of nonmelanoma skin cancer (NMSC). Bavinck et al[77] assessed the effect of acitretin on the development of NMSC in renal transplant patients. After 6 months of treatment, 2 of 19 patients (11%) in the acitretin group reported 2 new SCCs compared with 9 of 19 patients (47%) in the placebo group who reported 18 new SCCs. Multiple studies have reported similar results with acitretin.[78,79]

Biologics and other newer agents

Bongartz et al[80] found a 3-fold increase in the risk of developing all cancers with infliximab and adalimumab (odds ratio 3.3; 95% confidence interval 1.2-9.1). Recently, Asgari et al[81] showed that biologics increase the risk of NMSC by 42% (an 80% increase in SCC). In addition, there are several reports that strengthen the link between anti–TNF-α therapy and induction or reactivation of latent SCCs and keratoacanthomas.[82-91] The relationship between lymphoma and TNF-α inhibitors has also been documented in a few case reports.[92] In contrast, a systematic review of 32 randomized controlled trials and 6 open-label extensions reported that TNF-α inhibitors do not lead to significant increase in cancer risk, at least in the short term.[93] Animal studies of ustekinumab show a high risk of developing NMSCs with prolonged treatment.[94] Five years of follow-up data from the PHOENIX1/2 studies and safety data from the Psoriasis Longitudinal Assessment and Registry demonstrated low or no overall increased risk for malignancy with long-term exposure to ustekinumab.[95-97] A case of melanoma recurrence was reported in a patient on apremilast, but no direct causal association was proven.[98] There are not enough data on the malignancy potential of IL-17 and IL-23 inhibitors, but there have been no reported associations with malignancy so far.

Expert opinion

1. TNF-α inhibitors may increase the risk of NMSC, namely SCCs, but they do not increase the

overall risk of cancers. It is best to avoid anti—TNF-α agents in patients with concurrent malignancy or a history of malignancy, especially multiple cutaneous SCCs.
2. The clinical data for ustekinumab look promising, but caution needs to be exercised because it has demonstrated carcinogenic potential in animal models.
3. Data are limited for apremilast and IL-17 and IL-23 inhibitors, and more long-term studies are needed to assess their carcinogenic potential.
4. Acitretin has preventative effects on NMSCs and therefore is the preferred agent in patients with a high risk of skin cancers. Methotrexate and cyclosporine should be avoided in this setting.

OBESITY

Moderate to severe psoriasis is associated with the metabolic syndrome, which includes obesity, hyperlipidemia, and diabetes mellitus.[99] Patients with psoriasis tend to be more obese than age- and sex-matched individuals without psoriasis.[100,101]

Traditional agents

Nonalcoholic fatty liver disease has been found to be more common in obese patients with psoriasis than in the general population.[102] In addition, psoriasis is considered an independent predictor of advanced liver fibrosis regardless of other factors, such as age, body mass index (BMI), hypertension, and diabetes.[103] With methotrexate use, 96% of patients with coexisting risk factors of obesity, diabetes, and alcohol use developed hepatic fibrosis compared with 71% of patients with no risk factors.[104] Acitretin and cyclosporine can both cause hyperlipidemia. Moreover, obese patients require higher doses, which in turn leads to increased side effects.[105-108]

Biologics and other newer agents

All anti—TNF-α agents are used at fixed doses except infliximab, which is dosed by weight. Multiple studies have shown that the therapeutic response is better in patients with normal BMI versus higher BMI.[109-111] The Comparative Study of Humira versus Methotrexate versus Placebo in Psoriasis Patients study for adalimumab demonstrated a significant PASI 75 response rate (ie, a 75% reduction in PASI score from baseline) in obese patients, although this was lower than in normal and overweight subjects.[112] There is evidence that reduction in weight leads to a better response with TNF-α inhibitors.[113] Dosage of ustekinumab is based on body weight. Zhu et al[114] determined that body weight and diabetes are important covariates affecting ustekinumab's apparent clearance or volume of distribution.

IL-17 inhibitors are highly efficacious drugs regardless of body weight. However, normal weight patients tend to have a better response than overweight and obese patients. In a phase 2 trial of secukinumab, PASI 75 was 73% for patients who were >90 kg and 83% for those weighing <90 kg.[115] Phase 3 studies for ixekizumab (UNCOVER-1,2,3) have demonstrated its efficacy regardless of a patient's body weight.[116] Unlike TNF-α inhibitors, IL-17 inhibitors have not been observed to cause weight gain in clinical trials. Brodalumab demonstrated higher rates of PASI 75 and PASI 90 (ie, a 90% reduction in PASI score from baseline) at weeks 12 and 52 in nonobese patients as compared with obese patients in a phase 3 trial (AMAGINE 1).[117] Apremilast has been shown to cause weight loss in ESTEEM 1/2 and PALACE 3 trials, suggesting a potentially advantageous effect.[35,118,119] Weight-based data for IL-23 inhibitors are not yet available.

Expert opinion

1. Infliximab and ustekinumab are dosed based on weight and are ideal drugs to treat psoriasis in obese patients.
2. IL-17 inhibitors are highly effective regardless of a patient's weight but are shown to have even better clearance rates in nonobese patients. There are not enough weight data on IL-23 inhibitors, but they are highly efficacious agents nonetheless.
3. Apremilast can be used favorably in obese patients because weight loss is a noted side effect of this drug.
4. Methotrexate carries a higher risk of fatty liver and hepatic fibrosis in obese patients and therefore should be avoided. Acitretin and cyclosporine need to be used in higher doses in obese patients, leading to a higher incidence of side effects and potential for toxicity.

CARDIAC DISEASES

Gelfand et al[120] published the landmark study that identified psoriasis as an independent risk factor for cardiovascular diseases. Chronic inflammation is a hallmark for psoriasis and is also known to play an important role in atherosclerosis, which explains the increased risk of MACEs in patients with psoriasis.[121-124]

Traditional agents

Methotrexate reduces the incidence of cardiovascular diseases, but its long-term use leads to a higher

risk of end organ toxicity.[125] Acitretin causes hyperlipidemia,[126] but a study by Stern et al[127] showed no increase in risk of MACE with use of etretinate in patients with psoriasis. Cyclosporine leads to hypertension, hyperlipidemia, and is known to cause myocardial damage by generating reactive oxygen species.[128,129]

Biologics and other newer agents

Biologics act by reducing overall inflammation which leads to a reduction in the incidence of cardiovascular diseases as reported in various rheumatologic and psoriasis registries.[130] Wu and Poon[131] reported that hazard ratio of myocardial infarction for patients with psoriasis who were treated with TNF-α inhibitors compared with those not treated was 0.26 (95% CI 0.12-0.56; ie, a 74% lower risk of myocardial infarction compared with a control population. Psoriatic patients who do not respond to biologics show a minimal reduction in MACE risk.[132,133] Multiple cohort studies also suggest that biologics may have a cardioprotective effect, with an almost 50% reduction in the rate of myocardial infarction in patients with psoriasis who are treated with biologics.[134,135] Conversely, Bissonnette et al[136,137] reported no significant reduction in vascular inflammation in adalimumab-treated patients. Ustekinumab caused some concerns of increased MACE during initial analysis. However, a Psoriasis Longitudinal Assessment and Registry data–based safety surveillance study identified no increased risk of MACE with ustekinumab use.[138] There are not enough MACE data pertaining to apremilast, IL-17, and IL-23 inhibitors.

Expert opinion

1. TNF-α inhibitors are preferred systemic agents for treatment of psoriasis in patients with coexisting cardiovascular risk factors.
2. Ustekinumab has some potential cardioprotective benefit, but more long-term data are needed.
3. More data are needed for the use of apremilast, IL-17, and IL-23 inhibitors
4. Methotrexate has proven cardioprotective benefits but may cause end organ toxicity with long-term use. Cyclosporine and acitretin should be avoided because of concerns of hyperlipidemia and hypertension.

CONGESTIVE HEART FAILURE

The association between psoriasis and congestive heart failure (CHF) is unclear, but it is suggested that moderate to severe psoriasis increases the risk of heart failure.[139,140]

Traditional agents

Antiinflammatory effects of methotrexate can lead to improvement in New York Heart Association functional class and therefore overall quality of life.[141] The role of cyclosporine in CHF has not been assessed in patients with psoriasis, but there are no reports of CHF exacerbation in multiple studies in patients with end-stage heart failure after heart transplantation.[142-145] There are no reports of new onset CHF or exacerbation with acitretin use.

Biologics and other newer agents

There have been several conflicting case reports on anti–TNF-α agents and CHF.[146,147] The efficacy of infliximab was assessed in the Antihypertensive Treatment of Acute Cerebral Hemorrhage trial, where patients receiving high doses of infliximab (10 mg/kg) demonstrated worsening of heart failure. Contrarily, another study with etanercept has reported a dose-dependent improvement of ventricular function.[148] Specific data on other anti–TNF-α agents are limited. Long-term safety data on ustekinumab, apremilast, IL-17, and IL-23 inhibitors in CHF is also limited, but there have been no reports of CHF exacerbation with their use.

Expert opinion

1. Although controversial, the New York Heart Association recommendations for anti–TNF-α agents in patients with CHF are as follows[149,150]:
   - TNF-α inhibitors are contraindicated in class 3 or 4 CHF
   - Echocardiogram should be done before treatment initiation in class 1 or 2 CHF and TNF-α inhibitors should be avoided in patients with ejection fraction <50%
   - TNF-α inhibitors should be discontinued in patients with new onset CHF
2. Ustekinumab, apremilast, IL-17, and IL-23 inhibitors appear to be safe to use in CHF patients.
3. Methotrexate, cyclosporine, and acitretin can be used in patients with psoriasis who have CHF.

MULTIPLE SCLEROSIS

Recent Danish- and US-based studies reported a significant association between multiple sclerosis (MS) and psoriasis, although the precise mechanism of this association is still not clear.[151-153] In contrast, a few other studies did not identify any association between psoriasis and MS.[154,155]

Table I. Factors to consider when selecting systemic psoriasis treatment

Class of drugs	Drug/comorbidity	PsA	CD	CA	Obesity	Cardiac	CHF	MS	Lupus
TNF-α inhibitors	Etanercept	++	+	−	+	++	−/+	x	+/−
	Adalimumab	++	++	−	+	++	−/+	x	+/−
	Infliximab	++	++	−	++	++	−/+	x	+/−
	Certolizumab	++	++	−	+	++	−/+	x	+/−
	Golimumab	++	++	−	+	++	−/+	x	+/−
IL-12/23 inhibitor	Ustekinumab	+	++	+	++	+	++	+	+
IL-17 inhibitors									
Anti−IL-17A	Secukinumab	++	−	?/+	++	?	++	+	?/+
Anti−IL-17A	Ixekizumab	++	−	?/+	++	?	++	+	?/+
Anti−IL-17 receptor	Brodalumab	+	−	?/+	++	?	++	+	?/+
IL-23 inhibitors	Guselkumab	?	+	?/+	++	?	++	?/+	?/+
	Tildrakizumab	?	+	?/+	++	?	++	?/+	?/+
	Risankizumab	?	+	?/+	?	?	++	?/+	?/+
	Mirikizumab	?	+	?/+	?	?	++	?/+	?/+
Oral novel	Apremilast	+	+	?/+	++	?	++	?/+	+
Oral traditional	Methotrexate	+	+	−	x	++	++	+	+
	Cyclosporine	+/−	+	x	+	?/−	++	+	+/−
	Acitretin	+/−	+	++	+	?/−	++	+	+

Note: Two plus symbols (++) indicates preferred agents; one plus symbol (+) indicates that the agent can be used; one plus symbol and one minus symbol (+/−) indicate that the drug can be used but is controversial; one minus symbol and one plus symbol (−/+) indicates that the drug is not preferred but can be used; one question mark and one plus symbol (?/+) indicates that there are not enough data but that the drug is likely safe to use; one question mark (?) indicates that there are not enough data; one minus symbol (−) indicates that use of that drug is controversial because there are not enough data; and x indicates that a drug is contraindicated.
CA, Cancer; *CD*, Crohn's disease; *CHF*, congestive heart failure; *IL*, interleukin; *MS*, multiple sclerosis; *PsA*, psoriatic arthritis; *TNF-α*, tumor necrosis factor−α.

Traditional agents

Methotrexate and cyclosporine have been shown to improve the symptoms and reduce relapse rate of MS.[156-161] There are no available data on acitretin use in patients with MS.

Biologics and other newer agents

Demyelinating disorders, with an incidence of 0.02% to 0.2%, have been described with the use of etanercept, infliximab, adalimumab, and golimumab.[162-166] Therefore, TNF-α inhibitors are contraindicated in demyelinating diseases, including MS and Guillain−Barré syndrome.[167,168] Ustekinumab was tested in a phase II clinical trial for relapsing and remitting MS and did not demonstrate any benefit or harm.[169] Nevertheless, there are no reports of worsening of neurologic disease with ustekinumab. Secukinumab has been shown to significantly reduce the magnetic resonance imaging lesion activity in MS as compared with placebo. Additional studies are needed to confirm these findings, but IL-17 inhibitors appear to be safe in patients with neurologic diseases.[170] There are no data on apremilast and IL-23 inhibitors in neurologic diseases.

Expert opinion

1. TNF-α inhibitors are contraindicated in patients with MS and other neurologic disorders. Regular evaluation of neurologic signs and symptoms should be performed during treatment with this class of drugs.
2. Ustekinumab can be used in patients with MS as it does not improve or worsen MS.
3. IL-17 inhibitors can be used with some benefit in MS symptoms.
4. Data are limited for the traditional agents, apremilast and IL-23 inhibitors, but there are no reports of MS worsening with these drugs.

LUPUS

Psoriasis and lupus erythematosus (LE) are both immune-mediated diseases but their coexistence is rare. Zalla et al[171] reported that 0.69% of patients with psoriasis have SLE and 1.1% of patients with SLE have psoriasis.

Traditional agents

Methotrexate has demonstrated a significant reduction of cutaneous and articular activity in SLE with reductions in the SLE disease activity index

score.[172-174] Acitretin has been used successfully in the treatment of LE.[175,176] Cyclosporine is usually used in combination with steroids to treat cases of refractory lupus nephritis, skin disease, and hematologic involvement.[177-180]

Biologics and other newer agents

There is concern for development of de novo lupus or flare-up of lupus during treatment with TNF-α blockers.[181,182] There have been several reports of the development of DLE, SCLE, and drug-induced lupus with infliximab, etanercept, and adalimumab.[183-186] However, a recent study by Varada et al[187] reported a low incidence of lupus flare/patient-year with TNF-α blockers (0.92%). Many other studies have confirmed the low incidence of anti–TNF-α–induced lupus, reporting rates of 0.19% to 0.22% for infliximab, 0.18% for etanercept, and 0.10% for adalimumab.[188] It is suggested that drug-induced lupus involving anti–TNF-α agents be known as anti–TNF-α–induced lupus (ATIL). ATIL has a higher incidence of hypocomplementemia and high titers of anti-dsDNA antibody compared with drug-induced lupus, which has higher titers of antihistone antibodies. Renal and central nervous system involvement is also more common in ATIL.[182,189] Ustekinumab reportedly improves SLE symptoms, specifically oral ulcerations, anemia or thrombocytopenia, and lupus arthritis.[187,190] Apremilast has demonstrated significant reduction in DLE disease activity in a case series of 8 patients.[191] There are not enough data regarding the use of IL-17 and IL-23 inhibitors in patients with SLE, but no new cases of lupus induction or flare have been reported yet.

Expert opinion

1. Anti–TNF-α agents can be used watching out for lupus inductions and flare-up.
2. Ustekinumab emerges as the safest treatment option for concomitant lupus and psoriasis.
3. Data are limited for apremilast, IL-17, and IL-23 inhibitors, but there have been no reports of lupus induction or flare-ups.
4. Methotrexate and acitretin are good treatment options. Cyclosporine should be used only in severe or treatment refractory cases, as it is usually used with systemic corticosteroids.

In conclusion, it is important to understand how comorbidities adversely impact the overall quality of life and have substantial implications for psoriasis management. Practice gaps exist because of the scarcity of concise reviews addressing the newer therapeutic advancements and their role in different subpopulations of patients with psoriasis. We have attempted to provide a review of psoriasis management in the setting of commonly encountered clinical scenarios. A summary of our expert opinion is charted in Table I. The second article in this continuing medical education series discusses the use of systemic agents for psoriasis in distinct patient populations, including during pregnancy and in pediatric populations, and also in populations with chronic infections, such as hepatitis, HIV, and latent tuberculosis.

REFERENCES

1. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol*. 2017;76:377-390.
2. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol*. 2014;70:871-881. e1-30.
3. Villani AP, Rouzaud M, Sevrain M, et al. Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: systematic review and meta-analysis. *J Am Acad Dermatol*. 2015;73:242-248.
4. Dominguez-Rosado I, Moutinho V Jr, DeMatteo RP, Kingham TP, D'Angelica M, Brennan MF. Outcomes of the Memorial Sloan Kettering Cancer Center International General Surgical Oncology Fellowship. *J Am Coll Surg*. 2016;222:961-966.
5. Gladman DD, Stafford-Brady F, Chang CH, Lewandowski K, Russell ML. Longitudinal study of clinical and radiological progression in psoriatic arthritis. *J Rheumatol*. 1990;17:809-812.
6. McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology (Oxford)*. 2003;42:778-783.
7. Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis*. 2012;71:319-326.
8. Kingsley GH, Kowalczyk A, Taylor H, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology (Oxford)*. 2012;51:1368-1377.
9. Pincus T, Bergman MJ, Yazici Y. Limitations of clinical trials in chronic diseases: is the efficacy of methotrexate (MTX) underestimated in polyarticular psoriatic arthritis on the basis of limitations of clinical trials more than on limitations of MTX, as was seen in rheumatoid arthritis? *Clin Exp Rheumatol*. 2015;33(5 suppl 93):S82-S93.
10. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet*. 2000;356:385-390.
11. Gupta AK, Matteson EL, Ellis CN, et al. Cyclosporine in the treatment of psoriatic arthritis. *Arch Dermatol*. 1989;125:507-510.
12. Steinsson K, Jonsdottir I, Valdimarsson H. Cyclosporin A in psoriatic arthritis: an open study. *Ann Rheum Dis*. 1990;49:603-606.
13. Salvarani C, Macchioni P, Boiardi L, et al. Low dose cyclosporine A in psoriatic arthritis: relation between soluble

interleukin 2 receptors and response to therapy. *J Rheumatol*. 1992;19:74-79.
14. Mahrle G, Schulze HJ, Brautigam M, et al. Anti-inflammatory efficacy of low-dose cyclosporin A in psoriatic arthritis. A prospective multicentre study. *Br J Dermatol*. 1996;135: 752-757.
15. Fraser AD, van Kuijk AW, Westhovens R, et al. A randomised, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis*. 2005; 64:859-864.
16. D'Angelo S, Cutro MS, Lubrano E, et al. Combination therapy with ciclosporin and etanercept in patients with psoriatic arthritis. *Ann Rheum Dis*. 2010;69:934-935.
17. Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? *Ann Rheum Dis*. 2011;70:2152-2154.
18. Kirkham B, de Vlam K, Li W, et al. Early treatment of psoriatic arthritis is associated with improved patient-reported outcomes: findings from the etanercept PRESTA trial. *Clin Exp Rheumatol*. 2015;33:11-19.
19. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2005;52:3279-3289.
20. Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum*. 2009; 60:976-986.
21. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis*. 2014;73:48-55.
22. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis*. 2014;73:990-999.
23. Jones BB, Millsop JW, Walsh JA, Krueger GG, Callis Duffin K. Onset of psoriatic arthritis during ustekinumab treatment for psoriasis: a case series of seven patients. *Br J Dermatol*. 2015; 173:272-274.
24. Kavanaugh A, Krueger GG, Beutler A, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Ann Rheum Dis*. 2007;66: 498-505.
25. Mease PJ, Ory P, Sharp JT, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Ann Rheum Dis*. 2009;68:702-709.
26. Bonifati C, Graceffa D. How effective is ustekinumab in controlling psoriatic arthritis? *Dermatol Ther*. 2016;29:155-159.
27. McInnes IB, Sieper J, Braun J, et al. Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis*. 2014;73:349-356.
28. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med*. 2015;373:1329-1339.
29. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015; 386:1137-1146.
30. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet*. 2017;389:2317-2327.
31. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis*. 2017; 76:79-87.
32. Mease PJ, Genovese MC, Greenwald MW, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med*. 2014;370:2295-2306.
33. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis*. 2014;73:1020-1026.
34. Cutolo M, Myerson GE, Fleischmann RM, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol*. 2016;43:1724-1734.
35. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis*. 2016;75:1065-1073.
36. Pathan E, Abraham S, Van Rossen E, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. *Ann Rheum Dis*. 2013;72:1475-1480.
37. Mease P, Genovese MC, Gladstein G, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum*. 2011;63: 939-948.
38. Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol*. 2009; 129:1339-1350.
39. Rovedatti L, Kudo T, Biancheri P, et al. Differential regulation of interleukin 17 and interferon gamma production in inflammatory bowel disease. *Gut*. 2009;58:1629-1636.
40. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361:2066-2078.
41. Cohen AD, Dreiher J, Birkenfeld S. Psoriasis associated with ulcerative colitis and Crohn's disease. *J Eur Acad Dermatol Venereol*. 2009;23:561-565.
42. Li WQ, Han JL, Chan AT, Qureshi AA. Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. *Ann Rheum Dis*. 2013;72:1200-1205.
43. Tsai TF, Wang TS, Hung ST, et al. Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. *J Dermatol Sci*. 2011;63:40-46.
44. Edson-Heredia E, Zhu B, Lefevre C, et al. Prevalence and incidence rates of cardiovascular, autoimmune, and other diseases in patients with psoriatic or psoriatic arthritis: a

retrospective study using Clinical Practice Research Datalink. *J Eur Acad Dermatol Venereol*. 2015;29:955-963.
45. Wu JJ, Nguyen TU, Poon KY, Herrinton LJ. The association of psoriasis with autoimmune diseases. *J Am Acad Dermatol*. 2012;67:924-930.
46. Augustin M, Reich K, Glaeske G, Schaefer I, Radtke M. Co-morbidity and age-related prevalence of psoriasis: analysis of health insurance data in Germany. *Acta Derm Venereol*. 2010;90:147-151.
47. McDonald JW, Tsoulis DJ, Macdonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Database Syst Rev*. 2012;12:CD003459.
48. Feagan BG, McDonald JW, Rochon J, et al. Low-dose cyclosporine for the treatment of Crohn's disease. The Canadian Crohn's Relapse Prevention Trial Investigators. *N Engl J Med*. 1994;330:1846-1851.
49. Stange EF, Modigliani R, Pena AS, Wood AJ, Feutren G, Smith PR. European trial of cyclosporine in chronic active Crohn's disease: a 12-month study. The European Study Group. *Gastroenterology*. 1995;109:774-782.
50. Lee SY, Jamal MM, Nguyen ET, Bechtold ML, Nguyen DL. Does exposure to isotretinoin increase the risk for the development of inflammatory bowel disease? A meta-analysis. *Eur J Gastroenterol Hepatol*. 2016;28:210-216.
51. Tenner S. Isotretinoin and inflammatory bowel disease: trial lawyer misuse of science and FDA warnings. *Am J Gastroenterol*. 2014;109:570-571.
52. Isotretinoin, acne, and Crohn's disease: a convergence of bad skin, bad science, and bad litigation creates the perfect storm. *Gastroenterol Hepatol (N Y)*. 2013;9:752-755.
53. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359:1541-1549.
54. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350:876-885.
55. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130:323-333.
56. Sandborn WJ, Lee SD, Randall C, et al. Long-term safety and efficacy of certolizumab pegol in the treatment of Crohn's disease: 7-year results from the PRECiSE 3 study. *Aliment Pharmacol Ther*. 2014;40:903-916.
57. Sandborn WJ, Schreiber S, Hanauer SB, Colombel JF, Bloomfield R, Lichtenstein GR. Reinduction with certolizumab pegol in patients with relapsed Crohn's disease: results from the PRECiSE 4 Study. *Clin Gastroenterol Hepatol*. 2010;8:696-702.e1.
58. Osterman MT, Haynes K, Delzell E, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12:811-817.e3.
59. Kestens C, van Oijen MG, Mulder CL, et al. Adalimumab and infliximab are equally effective for Crohn's disease in patients not previously treated with anti-tumor necrosis factor-alpha agents. *Clin Gastroenterol Hepatol*. 2013;11:826-831.
60. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146:85-95.
61. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375:1946-1960.
62. van de Kerkhof PC, Griffiths CE, Reich K, et al. Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. *J Am Acad Dermatol*. 2016;75:83-98.e4.
63. 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.
64. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375:345-356.
65. Reich K, Leonardi C, Langley RG, et al. Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: a presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials. *J Am Acad Dermatol*. 2017;76:441-448.e2.
66. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med*. 2012;366:1181-1189.
67. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373:1318-1328.
68. Feagan BG, Sandborn WJ, D'Haens G, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet*. 2017;389:1699-1709.
69. Izzo AA, Mascolo N, Capasso F. Effect of selective phosphodiesterase inhibitors on synaptic transmission in the guinea-pig ileum. *Naunyn Schmiedebergs Arch Pharmacol*. 1998;357:677-681.
70. Salari-Sharif P, Abdollahi M. Phosphodiesterase 4 inhibitors in inflammatory bowel disease: a comprehensive review. *Curr Pharm Des*. 2010;16:3661-3667.
71. Nyfors A, Jensen H. Frequency of malignant neoplasms in 248 long-term methotrexate-treated psoriatics. A preliminary study. *Dermatologica*. 1983;167:260-261.
72. Ebeo CT, Girish MR, Byrd RP, Roy TM, Mehta JB. Methotrexate-induced pulmonary lymphoma. *Chest*. 2003;123:2150-2153.
73. Paul C, Le Tourneau A, Cayuela JM, et al. Epstein-Barr virus-associated lymphoproliferative disease during methotrexate therapy for psoriasis. *Arch Dermatol*. 1997;133:867-871.
74. Khopkar U, Bhor U. Hodgkin's lymphoma in a patient of psoriasis treated with long-term, low-dose methotrexate therapy. *Indian J Dermatol Venereol Leprol*. 2008;74:379-382.
75. Patel RV, Clark LN, Lebwohl M, Weinberg JM. Treatments for psoriasis and the risk of malignancy. *J Am Acad Dermatol*. 2009;60:1001-1017.
76. Paul CF, Ho VC, McGeown C, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol*. 2003;120:211-216.
77. Bavinck JN, Tieben LM, Van der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol*. 1995;13:1933-1938.
78. McKenna DB, Murphy GM. Skin cancer chemoprophylaxis in renal transplant recipients: 5 years of experience using low-dose acitretin. *Br J Dermatol*. 1999;140:656-660.
79. de Sevaux RG, Smit JV, de Jong EM, van de Kerkhof PC, Hoitsma AJ. Acitretin treatment of premalignant and malignant skin disorders in renal transplant recipients: clinical effects of a randomized trial comparing two doses of acitretin. *J Am Acad Dermatol*. 2003;49:407-412.

80. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295:2275-2285.
81. Asgari MM, Ray GT, Geier JL, Quesenberry CP. Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population. *J Am Acad Dermatol*. 2017;76:632-638.
82. Nannini C, Cantini F, Niccoli L, et al. Single-center series and systematic review of randomized controlled trials of malignancies in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis receiving anti-tumor necrosis factor alpha therapy: is there a need for more comprehensive screening procedures? *Arthritis Rheum*. 2009; 61:801-812.
83. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum*. 2007;56:2886-2895.
84. Brewer JD, Hoverson Schott AR, Roenigk RK. Multiple squamous cell carcinomas in the setting of psoriasis treated with etanercept: a report of four cases and review of the literature. *Int J Dermatol*. 2011;50:1555-1559.
85. Fryrear RS 2nd, Wiggins AK, Sangueza O, Yosipovitch G. Rapid onset of cutaneous squamous cell carcinoma of the penis in a patient with psoriasis on etanercept therapy. *J Am Acad Dermatol*. 2004;51:1026.
86. Ly L, Czarnecki D. The rapid onset of multiple squamous cell carcinomas during etanercept treatment for psoriasis. *Br J Dermatol*. 2007;157:1076-1078.
87. Smith KJ, Skelton HG. Rapid onset of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis after starting tumor necrosis factor alpha receptor IgG1-Fc fusion complex therapy. *J Am Acad Dermatol*. 2001;45:953-956.
88. Burge D. Etanercept and squamous cell carcinoma. *J Am Acad Dermatol*. 2003;49:358-359.
89. Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiol Drug Saf*. 2011;20:119-130.
90. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. *Ann Rheum Dis*. 2011;70:1895-1904.
91. Raaschou P, Simard JF, Holmqvist M, Askling J. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. *BMJ*. 2013;346:f1939.
92. Girard C, Guillot B, Bessis D. Gastric MALT lymphoma in a patient receiving infliximab for psoriasis. *Br J Dermatol*. 2008; 159:497-498.
93. Bonovas S, Minozzi S, Lytras T, et al. Risk of malignancies using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2016;15(suppl 1): 35-54.
94. Ustekinumab. new drug. Suspicion of carcinogenicity: too great a risk for psoriasis patients. *Prescrire Int*. 2009;18: 202-204.
95. Gordon KB, Papp KA, Langley RG, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (part II of II): results from analyses of infections and malignancy from pooled phase II and III clinical trials. *J Am Acad Dermatol*. 2012;66:742-751.
96. Papp KA, Griffiths CE, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Dermatol*. 2013; 168:844-854.
97. Fiorentino D, Ho V, Lebwohl MG, et al. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. *J Am Acad Dermatol*. 2017;77:845-854.e5.
98. Salopek TG. Recurrence of melanoma after starting apremilast for psoriasis. *Case Rep Dermatol*. 2017;9:108-111.
99. Gisondi P, Galvan A, Idolazzi L, Girolomoni G. Management of moderate to severe psoriasis in patients with metabolic comorbidities. *Front Med (Lausanne)*. 2015;2:1.
100. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. *Nutr Diabetes*. 2012;2: e54.
101. Fleming P, Kraft J, Gulliver WP, Lynde C. The relationship of obesity with the severity of psoriasis: a systematic review. *J Cutan Med Surg*. 2015;19:450-456.
102. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. *J Hepatol*. 2009;51:758-764.
103. Gisondi P, Barba E, Girolomoni G. Non-alcoholic fatty liver disease fibrosis score in patients with psoriasis. *J Eur Acad Dermatol Venereol*. 2016;30:282-287.
104. Rosenberg P, Urwitz H, Johannesson A, et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. *J Hepatol*. 2007; 46:1111-1118.
105. Nast A, Gisondi P, Ormerod AD, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris—update 2015—short version—EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2015;29:2277-2294.
106. Powles AV, Hardman CM, Porter WM, Cook T, Hulme B, Fry L. Renal function after 10 years' treatment with cyclosporin for psoriasis. *Br J Dermatol*. 1998;138:443-449.
107. Lowe NJ, Wieder JM, Rosenbach A, et al. Long-term low-dose cyclosporine therapy for severe psoriasis: effects on renal function and structure. *J Am Acad Dermatol*. 1996;35(5 pt 1): 710-719.
108. Gisondi P, Cazzaniga S, Chimenti S, et al. Metabolic abnormalities associated with initiation of systemic treatment for psoriasis: evidence from the Italian Psocare Registry. *J Eur Acad Dermatol Venereol*. 2013;27:e30-e41.
109. Gordon K, Korman N, Frankel E, et al. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. *J Am Acad Dermatol*. 2006;54(3 suppl 2):S101-S111.
110. Menter A, Gordon KB, Leonardi CL, Gu Y, Goldblum OM. Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis. *J Am Acad Dermatol*. 2010;63:448-456.
111. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2008;158:558-566.
112. Prussick R, Unnebrink K, Valdecantos WC. Efficacy of adalimumab compared with methotrexate or placebo stratified by baseline BMI in a randomized placebo-controlled trial in patients with psoriasis. *J Drugs Dermatol*. 2015;14:864-868.
113. Iannone F, Lopalco G, Rigante D, Orlando I, Cantarini L, Lapadula G. Impact of obesity on the clinical outcome of rheumatologic patients in biotherapy. *Autoimmun Rev*. 2016; 15:447-450.

114. Zhu Y, Hu C, Lu M, et al. Population pharmacokinetic modeling of ustekinumab, a human monoclonal antibody targeting IL-12/23p40, in patients with moderate to severe plaque psoriasis. *J Clin Pharmacol*. 2009;49:162-175.
115. Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *Br J Dermatol*. 2013;168:412-421.
116. Reich K, Puig L, Mallbris L, Zhang L, Osuntokun O, Leonardi C. The effect of bodyweight on the efficacy and safety of ixekizumab: results from an integrated database of three randomised, controlled phase 3 studies of patients with moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31:1196-1207.
117. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2016;175:273-286.
118. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol*. 2015;173:1387-1399.
119. Vujic I, Herman R, Sanlorenzo M, et al. Apremilast in psoriasis - a prospective real-world study. *J Eur Acad Dermatol Venereol*. 2018;32:254-259.
120. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296:1735-1741.
121. Gisondi P, Girolomoni G. Psoriasis and atherothrombotic diseases: disease-specific and non-disease-specific risk factors. *Semin Thromb Hemost*. 2009;35:313-324.
122. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. The inflammatory response in mild and in severe psoriasis. *Br J Dermatol*. 2004;150:917-928.
123. Vanizor Kural B, Orem A, Cimsit G, Uydu HA, Yandi YE, Alver A. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. *Clin Chim Acta*. 2003;332:23-30.
124. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685-1695.
125. Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol*. 2005;52:262-267.
126. Dunn LK, Gaar LR, Yentzer BA, O'Neill JL, Feldman SR. Acitretin in dermatology: a review. *J Drugs Dermatol*. 2011;10:772-782.
127. Stern RS, Fitzgerald E, Ellis CN, Lowe N, Goldfarb MT, Baughman RD. The safety of etretinate as long-term therapy for psoriasis: results of the etretinate follow-up study. *J Am Acad Dermatol*. 1995;33:44-52.
128. Rezzani R. Exploring cyclosporine A-side effects and the protective role-played by antioxidants: the morphological and immunohistochemical studies. *Histol Histopathol*. 2006;21:301-316.
129. Robert N, Wong GW, Wright JM. Effect of cyclosporine on blood pressure. *Cochrane Database Syst Rev*. 2010;1:CD007893.
130. Ahlehoff O, Skov L, Gislason G, et al. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study. *J Intern Med*. 2013;273:197-204.
131. Wu JJ, Poon KY. Association of gender, tumor necrosis factor inhibitor therapy, and myocardial infarction risk in patients with psoriasis. *J Am Acad Dermatol*. 2013;69:650-651.
132. Abuabara K, Lee H, Kimball AB. The effect of systemic psoriasis therapies on the incidence of myocardial infarction: a cohort study. *Br J Dermatol*. 2011;165:1066-1073.
133. Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. *JAMA*. 2011;306:864-871.
134. Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. *J Am Heart Assoc*. 2013;2:e000062.
135. Gulliver WP, Young HM, Bachelez H, Randell S, Gulliver S, Al-Mutairi N. Psoriasis patients treated with biologics and methotrexate have a reduced rate of myocardial infarction: a collaborative analysis using international cohorts. *J Cutan Med Surg*. 2016;20:550-554.
136. Bissonnette R, Tardif JC, Harel F, Pressacco J, Bolduc C, Guertin MC. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. *Circ Cardiovasc Imaging*. 2013;6:83-90.
137. Bissonnette R, Harel F, Krueger JG, et al. TNF-alpha antagonist and vascular inflammation in patients with psoriasis vulgaris: a randomized placebo-controlled study. *J Invest Dermatol*. 2017;137:1638-1645.
138. Papp K, Gottlieb AB, Naldi L, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Drugs Dermatol*. 2015;14:706-714.
139. Khalid U, Ahlehoff O, Gislason GH, et al. Psoriasis and risk of heart failure: a nationwide cohort study. *Eur J Heart Fail*. 2014;16:743-748.
140. Yang YW, Keller JJ, Lin HC. Medical comorbidity associated with psoriasis in adults: a population-based study. *Br J Dermatol*. 2011;165:1037-1043.
141. Gong K, Zhang Z, Sun X, et al. The nonspecific anti-inflammatory therapy with methotrexate for patients with chronic heart failure. *Am Heart J*. 2006;151:62-68.
142. Eisen HJ. Immunosuppression on the horizon. *Heart Fail Clin*. 2007;3:43-49.
143. Yerly P, Mach F, Kalangos A, et al. Monitoring and adjustment of immunosuppression after heart transplantation [in French]. *Rev Med Suisse*. 2009;5, 1214-1216, 1218-1220.
144. Groetzner J, Reichart B, Roemer U, et al. Cardiac transplantation in pediatric patients: fifteen-year experience of a single center. *Ann Thorac Surg*. 2005;79:53-60.
145. Tarone G, Balligand JL, Bauersachs J, et al. Targeting myocardial remodelling to develop novel therapies for heart failure: a position paper from the Working Group on Myocardial Function of the European Society of Cardiology. *Eur J Heart Fail*. 2014;16:494-508.
146. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med*. 2003;138:807-811.
147. Kleinbongard P, Schulz R, Heusch G. TNFalpha in myocardial ischemia/reperfusion, remodeling and heart failure. *Heart Fail Rev*. 2011;16:49-69.
148. Bozkurt B, Torre-Amione G, Warren MS, et al. Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure. *Circulation*. 2001;103:1044-1047.
149. Desai SB, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. *Best Pract Res Clin Rheumatol*. 2006;20:757-790.

150. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58:826-850.
151. Langer-Gould A, Albers KB, Van Den Eeden SK, Nelson LM. Autoimmune diseases prior to the diagnosis of multiple sclerosis: a population-based case-control study. *Mult Scler*. 2010;16:855-861.
152. Egeberg A, Mallbris L, Gislason GH, Skov L, Hansen PR. Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study. *J Invest Dermatol*. 2016; 136:93-98.
153. Guido N, Cices A, Ibler E, et al. Multiple sclerosis association with psoriasis: a large U.S. population, single centre, retrospective cross-sectional study. *J Eur Acad Dermatol Venereol*. 2017;31:e397-e398.
154. Edwards LJ, Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. *Mult Scler*. 2004;10:575-581.
155. Ramagopalan SV, Dyment DA, Valdar W, et al. Autoimmune disease in families with multiple sclerosis: a population-based study. *Lancet Neurol*. 2007;6:604-610.
156. Neumann JW, Ziegler DK. Therapeutic trial of immunosuppressive agents in multiple sclerosis. *Neurology*. 1972;22: 1268-1271.
157. Currier RD, Haerer AF, Meydrech EF. Low dose oral methotrexate treatment of multiple sclerosis: a pilot study. *J Neurol Neurosurg Psychiatry*. 1993;56:1217-1218.
158. Ashtari F, Savoj MR. Effects of low dose methotrexate on relapsing-remitting multiple sclerosis in comparison to interferon beta-1alpha: a randomized controlled trial. *J Res Med Sci*. 2011;16:457-462.
159. Goodkin DE, Rudick RA, VanderBrug Medendorp S, et al. Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol*. 1995;37:30-40.
160. Zhao GJ, Li DK, Wolinsky JS, et al. Clinical and magnetic resonance imaging changes correlate in a clinical trial monitoring cyclosporine therapy for multiple sclerosis. The MS Study Group. *J Neuroimaging*. 1997;7:1-7.
161. Paty DW, Li DK. Interferon beta-lb is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. 1993 [classical article]. *Neurology*. 2001;57(12 suppl 5):S10-S15.
162. Tristano AG. Neurological adverse events associated with anti-tumor necrosis factor alpha treatment. *J Neurol*. 2010; 257:1421-1431.
163. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum*. 2001;44:2862-2869.
164. Cruz Fernandez-Espartero M, Perez-Zafrilla B, Naranjo A, et al. Demyelinating disease in patients treated with TNF antagonists in rheumatology: data from BIOBADASER, a pharmacovigilance database, and a systematic review. *Semin Arthritis Rheum*. 2011;41:524-533.
165. Ramos-Casals M, Roberto Perez A, Diaz-Lagares C, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by biological agents: a double-edged sword? *Autoimmun Rev*. 2010;9:188-193.
166. Kay J, Fleischmann R, Keystone E, et al. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. *Ann Rheum Dis*. 2015;74:538-546.
167. Gomez-Gallego M, Meca-Lallana J, Fernandez-Barreiro A. Multiple sclerosis onset during etanercept treatment. *Eur Neurol*. 2008;59:91-93.
168. Caminero A, Comabella M, Montalban X. Tumor necrosis factor alpha (TNF-alpha), anti-TNF-alpha and demyelination revisited: an ongoing story. *J Neuroimmunol*. 2011;234:1-6.
169. Segal BM, Constantinescu CS, Raychaudhuri A, Kim L, Fidelus-Gort R, Kasper LH. 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;7:796-804.
170. Havrdova E, Belova A, Goloborodko A, et al. Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study. *J Neurol*. 2016;263:1287-1295.
171. Zalla MJ, Muller SA. The coexistence of psoriasis with lupus erythematosus and other photosensitive disorders. *Acta Derm Venereol Suppl (Stockh)*. 1996;195:1-15.
172. Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. *J Rheumatol*. 1999;26:1275-1279.
173. Al-Mutairi N, Rijhwani M, Nour-Eldin O. Hypertrophic lupus erythematosus treated successfully with acitretin as monotherapy. *J Dermatol*. 2005;32:482-486.
174. Fortin PR, Abrahamowicz M, Ferland D, Lacaille D, Smith CD, Zummer M. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2008; 59:1796-1804.
175. Rothenberg RJ, Graziano FM, Grandone JT, Goldberg JW, Bjarnason DF, Finesilver AG. The use of methotrexate in steroid-resistant systemic lupus erythematosus. *Arthritis Rheum*. 1988;31:612-615.
176. Gansauge S, Breitbart A, Rinaldi N, Schwarz-Eywill M. Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). *Ann Rheum Dis*. 1997;56:382-385.
177. Xiong W, Lahita RG. Pragmatic approaches to therapy for systemic lupus erythematosus. *Nat Rev Rheumatol*. 2014;10: 97-107.
178. Wada Y, Kotani T, Takeuchi T, et al. Therapeutic drug monitoring of cyclosporine microemulsion in patients with corticosteroid-resistant systemic lupus erythematosus. *Mod Rheumatol*. 2015;25:708-713.
179. Manger K, Kalden JR, Manger B. Cyclosporin A in the treatment of systemic lupus erythematosus: results of an open clinical study. *Br J Rheumatol*. 1996;35:669-675.
180. Sheikholeslami M, Hajialilo M, Rasi Hashemi SS, Malek Mahdavi A, Gojazadeh M, Khabbazi A. Low dose cyclosporine A in the treatment of resistant proliferative lupus nephritis. *Mod Rheumatol*. 2018;28:523-529.
181. Wetter DA, Davis MD. Lupus-like syndrome attributable to anti-tumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic. *Mayo Clin Proc*. 2009;84:979-984.
182. Williams EL, Gadola S, Edwards CJ. Anti-TNF-induced lupus. *Rheumatology (Oxford)*. 2009;48:716-720.
183. Soforo E, Baumgartner M, Francis L, Allam F, Phillips PE, Perl A. Induction of systemic lupus erythematosus with tumor necrosis factor blockers. *J Rheumatol*. 2010;37: 204-205.

184. Spillane AP, Xia Y, Sniezek PJ. Drug-induced lupus erythematosus in a patient treated with adalumimab. *J Am Acad Dermatol*. 2007;56:S114-S116.
185. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet*. 2002;359:579-580.
186. Jacob N, Jacob CO. On anti-tumor necrosis factor-induced systemic lupus erythematosus. *J Rheumatol*. 2010;37:3-5.
187. Varada S, Gottlieb AB, Merola JF, Saraiya AR, Tintle SJ. Treatment of coexistent psoriasis and lupus erythematosus. *J Am Acad Dermatol*. 2015;72:253-260.
188. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis*. 2006;65:889-894.
189. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. *Arthritis Res Ther*. 2005;7:R545-R551.
190. Winchester D, Duffin KC, Hansen C. Response to ustekinumab in a patient with both severe psoriasis and hypertrophic cutaneous lupus. *Lupus*. 2012;21:1007-1010.
191. De Souza A, Strober BE, Merola JF, Oliver S, Franks AG Jr. Apremilast for discoid lupus erythematosus: results of a phase 2, open-label, single-arm, pilot study. *J Drugs Dermatol*. 2012;11:1224-1226.