Management of psoriasis as a systemic disease: what is the evidence?

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Linked Comment: Gisondi. Br J Dermatol 2020; 182: 823–824.

Summary

Background Psoriasis is a chronic, systemic immune-mediated disease characterized by development of erythematous, indurated, scaly, pruritic and often painful skin plaques. Psoriasis pathogenesis is driven by proinflammatory cytokines and psoriasis is associated with increased risk for comorbidities, including, but not limited to, psoriatic arthritis, cardiovascular disease, diabetes mellitus, obesity, inflammatory bowel disease and nonalcoholic fatty liver disease compared with the general population.

Objectives To explore the pathophysiological relationship between psoriasis and its common comorbidities and discuss the need for new treatment paradigms that include strategies to reduce systemic inflammation in patients with moderate-to-severe psoriasis.

Methods This narrative review summarizes the published evidence related to the ability of biological therapies to ameliorate the consequences of systemic inflammation in patients with psoriasis.

Results Current evidence suggests that preventing damage associated with inflammation, and preventing development of future inflammatory damage and comorbidities, may be a potentially achievable treatment goal for many patients with moderate-to-severe plaque psoriasis when biological therapies are utilized early in the disease. Encouraging data from recent studies suggest that the loftier goal of reversing existing inflammatory damage and improving signs and symptoms of inflammatory comorbidities could also possibly be attainable.

Conclusions Results from ongoing prospective studies regarding the effects of biologics on markers of systemic inflammation in patients with psoriasis will strengthen the clinical evidence base that can be used to inform treatment decisions for patients with moderate-to-severe psoriasis.

What’s already known about this topic?

Psoriasis is a systemic inflammatory disease and treatments are needed to optimize patient outcomes.

What does this study add?

This review discusses new psoriasis treatment paradigms that may potentially reduce effects of systemic inflammation.

Evidence demonstrating that biological treatment may prevent or reverse inflammatory damage associated with psoriasis comorbidities is reviewed.
Psoriasis is an immune-mediated, chronic inflammatory condition affecting approximately 3% of adults and 0.1% of children and adolescents in the U.S.A. It is characterized by well-demarcated, erythematous plaques covered by silvery-white scales, typically occurring in a symmetrical distribution involving the elbows, knees, trunk and scalp. Psoriasis onset is triggered when genetic and/or environmental factors activate plasmacytoid dendritic cells, resulting in the production of numerous proinflammatory cytokines, including tumour necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-17, IL-22, IL-23 and IL-1β. Many of these cytokines stimulate keratinocyte hyperproliferation, which perpetuates a cycle of chronic inflammation.

In moderate-to-severe psoriasis, elevated levels of multiple proinflammatory cytokines are found not only in skin lesions, but also in the blood. Systemic elevations in these cytokines promote chronic subclinical inflammation (asymptomatic inflammation that can cause tissue damage over time) associated with comorbidities that disproportionately affect patients with psoriasis, including psoriatic arthritis (PsA), cardiovascular disease (CVD), diabetes mellitus, obesity, inflammatory bowel disease and nonalcoholic fatty liver disease (NAFLD) (Table 1).

It is hypothesized that early systemic treatment targeting proinflammatory cytokines associated with psoriasis pathogenesis will not only improve cutaneous symptoms but also reduce systemic inflammation, hence improving long-term outcomes through mitigation of comorbidity progression. This review explores the pathophysiological relationship between psoriasis and its common comorbidities, and discusses the need for new treatment paradigms that include strategies to reduce the effects of systemic inflammation in moderate-to-severe plaque psoriasis.

### Table 1 Comorbidities associated with psoriasis

| Comorbidity       | Increased risk with psoriasis                                      |
|-------------------|-------------------------------------------------------------------|
| CVDr              | Atherosclerosis                                                   |
|                   | • Moderate psoriasis (Adjusted OR 1.39, 95% CI 1.11–1.76)          |
|                   | • Severe psoriasis (Adjusted OR 1.81, 95% CI 1.25–2.63)            |
| Heart failure     |                                                                  |
|                   | • Severe psoriasis (Adjusted OR 2.98, 95% CI 1.37–6.49)            |
|                   | • Moderate psoriasis (Adjusted OR 0.77, 95% CI 0.37–1.59)          |
|                   | • Mild psoriasis (Adjusted OR 0.93, 95% CI 0.54–1.61)              |
| Diabetes mellitus | Mild psoriasis (IRR 1.49, 95% CI 1.43–1.56)                       |
|                   | Severe psoriasis (IRR 2.13, 95% CI 1.91–2.37)                      |
| Obesity           | Mild psoriasis (pooled OR 1.46, 95% CI 1.17–1.82)                  |
|                   | Moderate-to-severe psoriasis (pooled OR 2.23, 95% CI 1.63–3.05)    |
| NAFLD             | Overall (OR 2.15, 95% CI 1.57–2.96)                                |
|                   | Moderate-to-severe psoriasis (OR 2.07, 95% CI 1.59–2.71)           |
| PsA               | Affects 30% of patients with psoriasis                            |
| IBD               | Patients with psoriasis have a 2.9-fold higher risk of developing Crohn disease than the general population |

CI, confidence interval; CVDr, cardiovascular disease; IBD, inflammatory bowel disease; IRR, incidence rate ratio; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PsA, psoriatic arthritis.

### Psoriasis: a systemic inflammatory disease

Historically, psoriasis was considered a disease that was limited to the skin and was typically treated with topical agents or phototherapy. Although such therapies can provide effective relief of localized skin symptoms, they do little to affect underlying disease causes. With recent advances in understanding the inflammatory nature of psoriasis, research efforts have focused on elucidating the roles of specific proinflammatory cytokines that contribute to disease pathogenesis, with the goal of developing new targeted therapies.

Psoriasis develops when activated plasmacytoid dendritic cells produce the proinflammatory cytokine IFN-α, which activates myeloid dendritic cells in conjunction with IFN-γ, TNF-α, IL-1β and IL-6. These activated myeloid dendritic cells produce IL-12 and IL-23, which correspondingly activate T helper (Th)1 and Th17 cells. Once initiated, this cycle of inflammation continues chronically, as activated Th1 cells produce TNF-α and Th17 cells produce IL-17A, IL-17F and IL-22. These cytokines further activate keratinocytes that produce a variety of cytokines, chemokines and antimicrobial peptides that promote an ongoing proinflammatory response (Fig. 1). As psoriasis progresses, its systemic nature is evidenced by increased serum levels of multiple proinflammatory cytokines, including TNF-α, IFN-γ, IL-6, IL-8, IL-12, IL-17A and IL-18, in patients with psoriasis compared with healthy controls. Observations from 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) studies also validate the hypothesis that psoriasis is a systemic inflammatory disease. In these studies, patients with moderate-to-severe psoriasis demonstrate subclinical inflammation in the liver, joints and tendons, in addition to significantly increased global arterial and subcutaneous inflammation, and patients...
with mild psoriasis had subclinical inflammation in the aorta.\textsuperscript{20–22} Also, ultrasound of femoral arteries can improve detection of subclinical atherosclerosis in patients with moderate-to-severe psoriasis and insulin resistance helps to provide a better prediction of subclinical atherosclerosis than traditional CVD risk factors.\textsuperscript{23} Such observations have led to a better understanding of how a subset of inflammatory molecules diffuse into the systemic circulation and then to various organ systems; this may contribute to the pathology of common inflammatory comorbidities in psoriasis (Fig. 2).\textsuperscript{24} Table 2 highlights findings from recent studies showing that shared systemic inflammatory pathways contribute to the pathogenesis of both psoriasis and its comorbidities. Increased understanding of the roles of these pathogenic molecular pathways has enabled an appreciation of the systemic nature of psoriasis and given rise to the development of multiple biological agents that target key cytokines involved in the disease.\textsuperscript{17,18,25}

**Goals for treating systemic inflammation in psoriasis**

Studies in other immune-mediated inflammatory diseases (IMIDs), including Crohn disease and rheumatoid arthritis (RA), have demonstrated the significant benefits of early treatment with approved biologics to improve outcomes and suggest that similar approaches may be helpful in controlling systemic inflammation and optimizing long-term outcomes in psoriasis.\textsuperscript{15} Notably, several of the same biological agents are approved for the treatment of moderate-to-severe psoriasis and RA (etanercept, adalimumab, certolizumab and infliximab) and/or Crohn disease (adalimumab, infliximab, certolizumab and ustekinumab) owing to the centrality of their targets in disease pathogenesis.

As practitioners more readily recognize psoriasis as a systemic disease and place more emphasis on controlling systemic inflammation, treatment goals can be separated into two distinct categories based on the feasibility of achieving desired outcomes. The first and most practically implementable goal is potentially preventing damage associated with systemic inflammation while simultaneously potentially preventing the progression of psoriasis and its comorbidities. The second, perhaps loftier and more forward-thinking, goal is potentially reversing existing inflammatory damage and signs and symptoms of comorbidities.

**Goal 1: prevent damage associated with inflammation and prevent future damage/comorbidities**

Numerous biomarkers of inflammation have been identified.\textsuperscript{26} Some of the most commonly utilized markers of inflammatory damage and cardiovascular risk in active psoriasis include C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).\textsuperscript{26} CRP levels are positively correlated with disease severity as measured by the Psoriasis Area and Severity Index
CRP is also an independent predictor of CVD risk and is implicated in the development of atherosclerotic lesions because it reduces expression of nitric oxide synthase and prostacyclin synthase, binds low-density lipoprotein cholesterol stimulating its uptake by macrophages and upregulates expression of adhesion molecules on endothelial cells. As levels of CRP decrease, cardiovascular risk lowers. However, there is evidence that questions the clinical usefulness of CRP for evaluating cardiovascular risk among individuals with inflammatory conditions such as psoriasis, indicating a need for alternative CVD risk biomarkers in patients with underlying inflammatory conditions.

Treatment with biological agents decreases systemic inflammation as measured by the ESR and CRP levels in several different disease states. For example, TNF-α inhibitors significantly reduce both ESR and CRP levels in RA. TNF-α inhibitors also significantly reduce CRP levels in patients who have either metabolic syndrome or Crohn disease. Similarly, the IL-12/23 inhibitor ustekinumab reduces ESR and CRP levels in Crohn disease, and the IL-17A inhibitor secukinumab reduces CRP levels in ankylosing spondylitis and reduces ESR levels in PsA. In patients with moderate-to-severe psoriasis treated with systemic therapies, including methotrexate, adalimumab, etanercept, infliximab and ixekizumab, studies have reported reductions in ESR and/or CRP levels.

Data from retrospective studies support the concept that certain biological agents targeting relevant proinflammatory cytokines involved in psoriasis pathogenesis may be the best treatment options to reduce the likelihood that patients with psoriasis will develop CVD. A large U.S. retrospective analysis found that patients receiving TNF-α inhibitors (etanercept, infliximab or adalimumab; percentages not specified) had significantly lower risks for myocardial infarction (MI) compared with patients receiving topical therapies [adjusted odds ratio 0.50, 95% confidence interval (CI) 0.32–0.79].48 and that treatment with these therapies decreased the risk of major cardiovascular events compared with methotrexate over 12 months of follow-up [adjusted hazard ratio (HR) 0.55, P < 0.001].49 Furthermore, over 24 months of follow-up, cumulative exposure to TNF-α inhibitors was associated with an 11% reduction in cardiovascular risk for every 6 months of treatment (P = 0.02).49 Another retrospective study utilizing a U.S. administrative claims database that included information from approximately 25 million patients and their dependents, compared over 11,000 patients with psoriasis

[Fig 2. Psoriasis. Comorbidities and key inflammatory cytokines. IFN, interferon; IL, interleukin; TNF, tumour necrosis factor.]
who were given TNF-α inhibitors with over 12,000 patients with psoriasis who were treated with phototherapy. They found that the TNF inhibitor cohort had a lower risk for major cardiovascular events when compared with the phototherapy cohort (adjusted HR 0.77, 95% CI 0.60–0.99; P = 0.046). Similarly, another large retrospective U.S. study with information from over 7.5 million patients with a mean follow-up time of 4.7 years found that individuals with psoriasis who received TNF-α inhibitors had a lower risk for major cardiovascular events than those receiving oral/phototherapy or topical therapy. In a systematic review and meta-analysis of patients with psoriasis and/or PsA, systemic therapy was associated with a significantly decreased risk of cardiovascular events compared with no systemic therapy or topical therapy. Importantly, a prospective study of 220 patients with moderate psoriasis found that improvement in PASI score, predominantly via treatment with TNF-α inhibitors (particular agents were unspecified), was associated with reduced aortic vascular inflammation measured using 18F-FDG PET/CT.

Although most research on the cardiovascular effects of treatment with TNF-α inhibitors in psoriasis has reported improvements in outcomes, not all studies suggest a positive correlation between treatment with biological agents and a reduced cardiovascular risk. A retrospective study of over 25,000 patients with moderate-to-severe psoriasis evaluated those treated with systemic therapies, including methotrexate, ciclosporin, alefacept, efalizumab, adalimumab, etanercept and infliximab, and compared them with patients who received ultraviolet B phototherapy. In this study, no significant difference was found in overall MI risk between the two groups (adjusted HR 1.33, 95% CI 0.90–1.96). Additionally, a retrospective study of 6,902 patients with severe psoriasis

| Comorbidity | Evidence of shared systemic inflammatory pathways |
|-------------|--------------------------------------------------|
| **Atherosclerosis** | IL-17A contributes to atherosclerotic lesion progression and plaque instability in murine models |
| | ACS is associated with upregulation of IL-17 and T helper (Th)17 cells. Th17 cells upregulate the number of IL-17 receptors on endothelial cells and vascular smooth muscle cells |
| | Cytokine product of Th1 cells (i.e. TNF-α) promotes endothelial dysfunction and movement of T cells to atherosclerotic plaques |
| | Patients with psoriasis have increased levels of markers of platelet activation (spontaneous platelet hyperaggregability, mean platelet volume, plasma levels of β-thromboglobulin and platelet factor 4), which are reduced on psoriasis clearance |
| **Heart failure** | Increased serum/plasma levels of TNF-α and IL-6 |
| | Levels of TNF-α are directly related to the New York Heart Association functional class |
| | Overall functional status in patients with CHF is inversely associated with levels of IL-6 |
| **Diabetes mellitus** | TNF-α promotes insulin resistance by reducing tyrosine kinase activity of the insulin receptor |
| | High serum levels of IL-6 (in conjunction with IL-1β), IL-8, IL-17 and IL-18 are found in diabetes and considered to contribute to insulin resistance |
| **Obesity** | Adipose tissue of individuals with obesity promotes the development of Th17 cells |
| | IL-17A expression is upregulated in obesity |
| | Other cytokines, such as TNF-α and IL-6, contribute to the proinflammatory state of obesity |
| **NAFLD** | TNF-α exacerbates hepatic insulin resistance, resulting in increased FFA synthesis and decreased FFA oxidation, thereby promoting hepatic steatosis |
| **PsA** | IL-23 and downstream cytokines IL-17 and IL-22 promote enthesitis in murine models |
| | Increased concentrations of Th17 cells, IL-17RA, IL-17A, TNF-α and IL-1 in the synovium of patients with PsA |
| | IL-17 and IL-22 linked to pannus formation in the joint, joint erosion and new bone formation |
| **IBD** | Mediated by Th1 cells and their cytokine products (i.e. TNF-α and IFN-γ) |
| | Increased levels of IL-17 and IL-23 found in the intestinal lamina propria of patients with Crohn disease |
reported similar risk for cardiovascular events with TNF-α or IL-12/23 inhibition (adjusted HR 0.58, 95% CI 0.30–1.10) compared with methotrexate (adjusted HR 0.53, 95% CI 0.34–0.83).

There have also been two small prospective studies of treatment with adalimumab in moderate-to-severe psoriasis. One study evaluated the effects of adalimumab compared with placebo for 16 weeks followed by open-label adalimumab treatment for 1 year. The other study examined adalimumab, phototherapy and placebo for 12 weeks followed by open-label adalimumab therapy for 1 year. Neither study demonstrated reduced vascular inflammation in the patients treated with adalimumab compared with placebo either at 12 weeks or 16 weeks or with phototherapy at 12 weeks as measured by 18F-FDG PET/CT. However, one of these studies evaluated several biomarkers and found decreased levels of glycoprotein acetylation, a novel composite biomarker of systemic inflammation, in patients treated with adalimumab compared with those treated with phototherapy. Additionally, a small prospective study of ustekinumab in a Korean population observed significantly decreased vascular inflammation in individuals who achieved ≥75% improvement in PASI over a mean treatment period of 5 months. Ongoing prospective studies include Vascular Inflammation In Psoriasis (VIP) trials that are currently evaluating the effects of ustekinumab (VIP-U; NCT02187172), secukinumab (VIP-S; NCT02690701) and apremilast (VIP-A; NCT03082729) on aortic inflammation as measured by 18F-FDG PET/CT and on levels of biomarkers associated with metabolic and cardiovascular risk. Results from studies of biological agents in IMIDs other than psoriasis support the hypothesis that biological agents can reduce systemic inflammation and prevent cardiovascular damage.

In addition to having the potential to prevent damage associated with vascular inflammation and preventing CVD, treatment with TNF-α inhibitors may play an important role in reducing inflammatory damage in other psoriasis comorbidities. In patients with psoriasis, increased systemic inflammation and dysregulation of adipokines, including leptin, resistin and adiponectin, increase the risk for insulin resistance that can progress to the development of diabetes mellitus and metabolic syndrome. This risk increases with psoriasis severity and decreases with TNF-α inhibitor therapy. In a small study (N = 89) that compared treatment with etanercept vs. psoralen and ultraviolet A (PUVA) therapy in moderate-to-severe psoriasis, NAFLD and metabolic syndrome, Campanati et al. observed that etanercept therapy was associated with significant reductions in transaminases, CRP and fasting insulin, and an increase in insulin sensitivity, whereas treatment with PUVA did not lead to significant reductions in these markers. These results support the concept that treatment with etanercept may have a more beneficial role than traditional therapies in preventing the progression of NAFLD to hepatic fibrosis via both its anti-inflammatory and glucose homeostatic properties.

Obesity is a well-known comorbidity of psoriasis, and in obesity, as in psoriasis and PsA, there is dysregulation of the levels and/or functions of ILs, TNF-α and other adipocytokines. However, a possible role for biological agents in mitigating obesity in psoriasis has not been observed to date. In fact, TNF-α inhibitors have induced modest weight gain in patients with moderate-to-severe psoriasis. No evidence of clinically significant weight gain has been reported in studies of ustekinumab or ixekizumab in moderate-to-severe psoriasis.

The ongoing ObePso-S trial (NCT03055494) is prospectively exploring the effects of IL-17A inhibition with the use of secukinumab on adipose tissue and skin inflammation in moderate-to-severe psoriasis.

Goal 2: reverse existing damage/comorbid conditions caused by inflammation

Evidence supporting the reversal of existing damage and/or comorbid conditions caused by systemic inflammation in patients with psoriasis is encouraging but not as well developed as evidence supporting the first stated goal of preventing damage and preventing future comorbidities. A study of ustekinumab treatment in patients with moderate-to-severe psoriasis (N = 46) showed regression of subclinical inflammatory enthesal and synovial abnormalities, suggesting the possibility that PsA development could be inhibited by biological treatment of psoriasis. Additionally, a study of 105 patients with varying degrees of psoriasis severity used CT angiography to show that treatment with systemic or biological agents was associated with improvement in noncalcified coronary plaque burden.

Furthermore, a study of 53 patients with moderate-to-severe psoriasis reported that methotrexate and ustekinumab significantly decreased carotid intima-media thickness levels. Other studies have shown improvement in measures of cardiovascular function with systemic psoriasis therapies. The effect of secukinumab on endothelial dysfunction in moderate-to-severe psoriasis without severe CVD is currently being evaluated in the prospective CARIMA study (NCT02559622).

Although it was hypothesized in most of these studies that the use of systemic anti-inflammatory treatment in psoriasis would lead to a decrease in the severity of comorbidities, studies published to date have been limited in size and scope, and larger well-designed studies are needed to provide a definitive link between these types of improvements and reductions in systemic inflammation. Overall, these findings are encouraging and suggest that early treatment with biologics has the potential, at least in the short term, to reverse damage caused by inflammatory comorbidities associated with psoriasis.

Discussion

Given the breadth of data indicating that psoriasis is a systemic disease and should be managed as such, it seems clear that systemic treatments are needed to optimize patient outcomes. Two goals were set forth to guide practitioners towards effective management of systemic inflammation in psoriasis. Based on the available evidence, the first goal – to prevent damage...
associated with inflammation and prevent future damage/comorbidities – appears to be attainable for many patients with the use of biological agent therapy early in the course of disease, which targets the appropriate proinflammatory cytokines. The second, loftier, goal – to reverse existing damage/comorbidity conditions caused by inflammation – has less evidence supporting its attainability. However, results from several studies in both animals and humans suggest that reversing damage may be more achievable than practitioners currently appreciate. The advancement of research on new biomarkers, which could improve either earlier diagnosis of comorbidities or clinical evaluation of comorbidities, may help practitioners better evaluate patient response to systemic therapies. In order to provide further support for the attainability of these treatment goals, efforts to collect prospective data are underway. Results from these prospective trials are expected to deliver important insights into the role that biological agents may play in treating systemic inflammation associated with psoriasis.

Acknowledgments

Technical assistance with editing and styling of the manuscript for submission was provided by Oxford PharmaGenesis Inc. and was funded by Novartis Pharmaceuticals Corporation. The author was fully responsible for all content and editorial decisions and received no financial support or other form of compensation related to the development of this manuscript.

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