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

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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.[1,2] 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.[3] 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.[4] Many of these cytokines stimulate keratinocyte hyperproliferation, which perpetuates a cycle of chronic inflammation.[5]

In moderate-to-severe psoriasis, elevated levels of multiple proinflammatory cytokines are found not only in skin lesions, but also in the blood.[6–9] 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).[10–14]

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.[15] 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.

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.[16] 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.[4,17,18]

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.[19] These activated myeloid dendritic cells produce IL-12 and IL-23, which correspondingly activate T helper (Th)1 and Th17 cells.[19] 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.[19] These cytokines further activate keratinocytes that produce a variety of cytokines, chemokines and antimicrobial peptides that promote an ongoing proinflammatory response (Fig. 1).[19]

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.[6–9] Observations from ^{18}F-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

Table 1 Comorbidities associated with psoriasis

Comorbidity	Increased risk with psoriasis
CVD[77]	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[78]	Mild psoriasis (IRR 1·49, 95% CI 1·43–1·56) Severe psoriasis (IRR 2·13, 95% CI 1·91–2·37)
Obesity[79]	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[11]	Overall (OR 2·15, 95% CI 1·57–2·94) Moderate-to-severe psoriasis (OR 2·07, 95% CI 1·59–2·71)
PsA[80]	Affects 30% of patients with psoriasis
IBD[81]	Patients with psoriasis have a 2·9-fold higher risk of developing Crohn disease than the general population

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

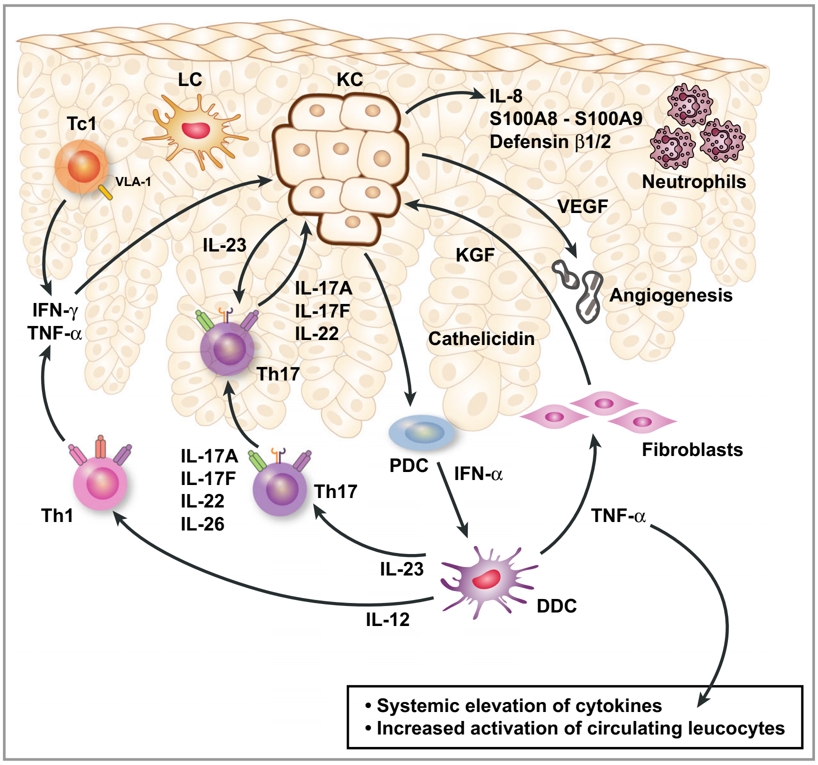

Fig 1. Psoriasis. Systemic inflammation. DDC, dermal dendritic cell; IFN, interferon; IL, interleukin; KC, keratinocyte; KGF, keratinocyte growth factor; LC, lymphocyte; PDC, plasmacytoid dendritic cell; Tc, cytotoxic T cell; Th, T helper cell; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; VLA, very late antigen. Adapted from Di Cesare *et al.*,[76] with permission from Elsevier.

with mild psoriasis had subclinical inflammation in the aorta.[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.[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).[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.[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.[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.[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).[26] CRP levels are positively correlated with disease severity as measured by the Psoriasis Area and Severity Index

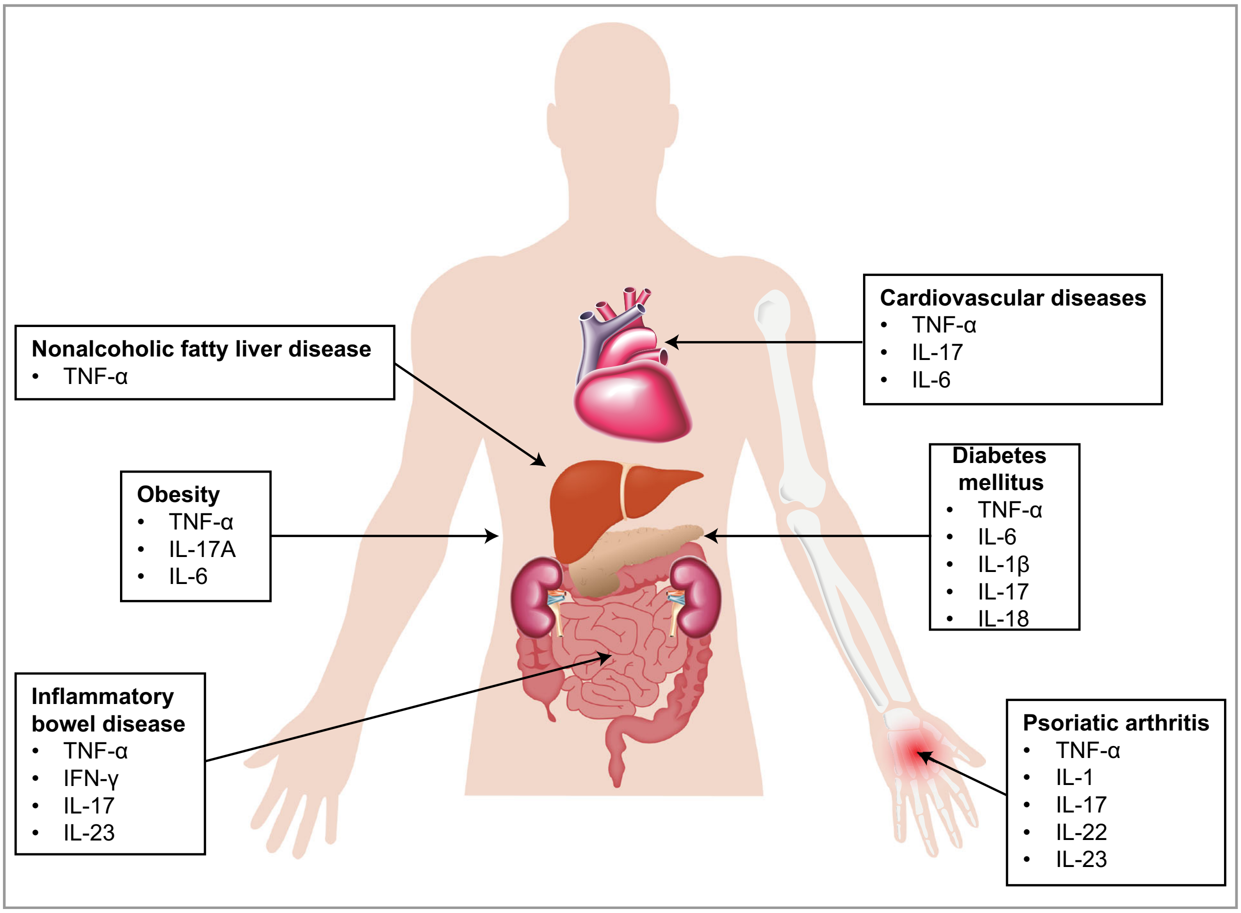

Fig 2. Psoriasis. Comorbidities and key inflammatory cytokines. IFN, interferon; IL, interleukin; TNF, tumour necrosis factor.

(PASI).[27,28] 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.[29] As levels of CRP decrease, cardiovascular risk lowers.[29] 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.[30,31]

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.[32,33] TNF-α inhibitors also significantly reduce CRP levels in patients who have either metabolic syndrome or Crohn disease.[34,35] Similarly, the IL-12/23 inhibitor ustekinumab reduces ESR and CRP levels in Crohn disease,[36] and the IL-17A inhibitor secukinumab reduces CRP levels in ankylosing spondylitis and reduces ESR levels in PsA.[37,38] 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.[39–47]

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 of cardiovascular event rates in patients with psoriasis (severity not reported) 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, $P < 0{\cdot}001$].[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 ($P = 0{\cdot}02$).[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

Table 2 Pathogenesis of psoriasis comorbidities

Comorbidity	Evidence of shared systemic inflammatory pathways
CVD[25,82–86]	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[87]	• 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[88–90]	• 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[91]	• TNF-α exacerbates hepatic insulin resistance, resulting in increased FFA synthesis and decreased FFA oxidation, thereby promoting hepatic steatosis
PsA[92–98]	• 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[99]	Crohn disease
	• 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 propia of patients with Crohn disease

ACS, acute coronary syndrome; CHF, congestive heart failure; CVD, cardiovascular disease; FFA, free fatty acid; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; NAFLD, nonalcoholic fatty liver disease; PsA, psoriatic arthritis; TNF, tumour necrosis factor.

who were given TNF-α inhibitors with over 12 000 patients with psoriasis who were treated with phototherapy.[50] 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.[51] 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.[52] 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 ^{18}F-FDG PET/CT.[53]

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).[54] Additionally, a retrospective study of 6902 patients with severe psoriasis 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).[55]

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.[56] The other study examined adalimumab, phototherapy and placebo for 12 weeks followed by open-label adalimumab therapy for 1 year.[57] Neither study demonstrated reduced vascular inflammation in the patients treated with adalimumab compared with placebo either at 12 weeks[57] or 16 weeks[56] or with phototherapy at 12 weeks[57] as measured by ^{18}F-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.[57] 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.[58] 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 ^{18}F-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.[59,60]

In addition to having the potential to prevent damage associated with vascular inflammation and preventing CVD,[48,49,53] 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 adipocytokines, including leptin, resistin and adiponectin, increase the risk for insulin resistance that can progress to the development of diabetes mellitus and metabolic syndrome.[25,61] This risk increases with psoriasis severity and decreases with TNF-α inhibitor therapy.[44,62,63] 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.[62] 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.[25] 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.[64–67] No evidence of clinically significant weight gain has been reported in studies of ustekinumab or ixekizumab in moderate-to-severe psoriasis.[67,68] 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 entheseal and synovial abnormalities, suggesting the possibility that PsA development could be inhibited by biological treatment of psoriasis.[69] 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.[70] Furthermore, a study of 53 patients with moderate-to-severe psoriasis reported that methotrexate and ustekinumab significantly decreased carotid intima-media thickness levels.[71] Other studies have shown improvement in measures of cardiovascular function with systemic psoriasis therapies.[72–75] 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/comorbid 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.

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References

1 Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol* 2014; **70**:512–16.
2 Paller AS, Singh R, Cloutier M *et al.* Prevalence of psoriasis in children and adolescents in the United States: a claims-based analysis. *J Drugs Dermatol* 2018; **17**:187–94.
3 Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; **370**:263–71.
4 Mahil SK, Capon F, Barker JN. Update on psoriasis immunopathogenesis and targeted immunotherapy. *Semin Immunopathol* 2016; **38**:11–27.
5 Swindell WR, Johnston A, Xing X *et al.* Modulation of epidermal transcription circuits in psoriasis: new links between inflammation and hyperproliferation. *PLOS ONE* 2013; **8**:e79253.
6 Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-α, IFN-γ, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm* 2005; **2005**:273–9.
7 Suárez-Fariñas M, Li K, Fuentes-Duculan J *et al.* Expanding the psoriasis disease profile: interrogation of the skin and serum of patients with moderate-to-severe psoriasis. *J Invest Dermatol* 2012; **132**:2552–64.
8 de Oliveira PS, Cardoso PR, Lima EV *et al.* IL-17A, IL-22, IL-6, and IL-21 serum levels in plaque-type psoriasis in Brazilian patients. *Mediators Inflamm* 2015; **2015**:819149.
9 Kolbinger F, Loesche C, Valentin MA *et al.* β-Defensin 2 is a responsive biomarker of IL-17A-driven skin pathology in patients with psoriasis. *J Allergy Clin Immunol* 2017; **139**:923–32.e8.
10 Egeberg A, Mallbris L, Warren RB *et al.* Association between psoriasis and inflammatory bowel disease: a Danish nationwide cohort study. *Br J Dermatol* 2016; **175**:487–92.
11 Candia R, Ruiz A, Torres-Robles R *et al.* Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2015; **29**:656–62.
12 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**:450–6.
13 Faustini F, Simon D, Oliveira I *et al.* Subclinical joint inflammation in patients with psoriasis without concomitant psoriatic arthritis: a cross-sectional and longitudinal analysis. *Ann Rheum Dis* 2016; **75**:2068–74.
14 Takeshita J, Grewal S, Langan SM *et al.* Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol* 2017; **76**:377–90.
15 Girolomoni G, Griffiths CE, Krueger J *et al.* Early intervention in psoriasis and immune-mediated inflammatory diseases: a hypothesis paper. *J Dermatolog Treat* 2015; **26**:103–12.
16 Boehncke WH, Boehncke S. More than skin-deep: the many dimensions of the psoriatic disease. *Swiss Med Wkly* 2014; **144**:w13968.
17 Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. *Cytokine* 2015; **73**:342–50.
18 Mak RK, Hundhausen C, Nestle FO. Progress in understanding the immunopathogenesis of psoriasis. *Actas Dermosifiliogr* 2009; **100** (Suppl. 2):2–13.
19 Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**:496–509.
20 Mehta NN, Yu Y, Saboury B *et al.* Systemic and vascular inflammation in patients with moderate to severe psoriasis as measured by [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT): a pilot study. *Arch Dermatol* 2011; **147**:1031–9.
21 Youn SW, Kang SY, Kim SA *et al.* Subclinical systemic and vascular inflammation detected by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with mild psoriasis. *J Dermatol* 2015; **42**:559–66.
22 Hjuler KF, Gormsen LC, Vendelbo MH *et al.* Increased global arterial and subcutaneous adipose tissue inflammation in patients with moderate-to-severe psoriasis. *Br J Dermatol* 2017; **176**:732–40.
23 Gonzalez-Cantero A, Gonzalez-Cantero J, Sanchez-Moya AI *et al.* Subclinical atherosclerosis in psoriasis. Usefulness of femoral artery ultrasound for the diagnosis, and analysis of its relationship with insulin resistance. *PLOS ONE* 2019; **14**:e0211808.
24 Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol* 2014; **32**:227–55.
25 Davidovici BB, Sattar N, Prinz J *et al.* Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. *J Invest Dermatol* 2010; **130**:1785–96.
26 Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999; **340**:448–54.
27 Vadakayil AR, Dandekeri S, Kambil SM, Ali NM *et al.* Role of C-reactive protein as a marker of disease severity and cardiovascular risk in patients with psoriasis. *Indian Dermatol Online J* 2015; **6**:322–5.
28 Coimbra S, Oliveira H, Reis F *et al.* C-reactive protein and leucocyte activation in psoriasis vulgaris according to severity and therapy. *J Eur Acad Dermatol Venereol* 2010; **24**:789–96.
29 Shrivastava AK, Singh HV, Raizada A, Singh SK. C-reative protein, inflammation and coronary heart disease. *Egypt Heart J* 2015; **67**:89–97.
30 Staniak HL, Bittencourt MS, de Souza Santos I *et al.* Association between psoriasis and coronary calcium score. *Atherosclerosis* 2014; **237**:847–52.
31 Joshi AA, Lerman JB, Aberra TM *et al.* GlycA is a novel biomarker of inflammation and subclinical cardiovascular disease in psoriasis. *Circ Res* 2016; **119**:1242–53.

32 Popa C, Netea MG, Radstake T *et al*. Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005; **64**:303–5.
33 Del Porto F, Laganà B, Lai S *et al*. Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. *Rheumatology (Oxford)* 2007; **46**:1111–15.
34 Bernstein LE, Berry J, Kim S *et al*. Effects of etanercept in patients with the metabolic syndrome. *Arch Intern Med* 2006; **166**:902–8.
35 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**:323–33; quiz 591.
36 Harris KA, Horst S, Gadani A *et al*. Patients with refractory Crohn's disease successfully treated with ustekinumab. *Inflamm Bowel Dis* 2016; **22**:397–401.
37 Baeten D, Baraliakos X, Braun J *et al*. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2013; **382**:1705–13.
38 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**:349–56.
39 Strober B, Teller C, Yamauchi P *et al*. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. *Br J Dermatol* 2008; **159**:322–30.
40 Zamanian A, Ehsani AH, Darvari SB *et al*. Trend of C-reactive protein and erythrocyte sedimentation rates in psoriatic patients on treatment of standard protocol of infliximab. *Galen Medical Journal* 2015; **4**:8–13.
41 Montaudié H, Albert-Sabonnadière C, Acquacalda E *et al*. Impact of systemic treatment of psoriasis on inflammatory parameters and markers of comorbidities and cardiovascular risk: results of a prospective longitudinal observational study. *J Eur Acad Dermatol Venereol* 2014; **28**:1186–91.
42 Griffiths CEM, Fava M, Miller AH *et al*. Impact of ixekizumab treatment on depressive symptoms and systemic inflammation in patients with moderate-to-severe psoriasis: an integrated analysis of three phase 3 clinical studies. *Psychother Psychosom* 2017; **86**:260–7.
43 Asahina A, Umezawa Y, Yanaba K, Nakagawa H. Serum C-reactive protein levels in Japanese patients with psoriasis and psoriatic arthritis: long-term differential effects of biologics. *J Dermatol* 2016; **43**:779–84.
44 Pina T, Armesto S, Lopez-Mejias R *et al*. Anti-TNF-alpha therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* 2015; **29**:1325–30.
45 Strober BE, Poulin Y, Teller C *et al*. Changes in C-reactive protein in patients with moderate-to-severe psoriasis switched to adalimumab therapy after suboptimal response to etanercept, methotrexate or phototherapy. *J Eur Acad Dermatol Venereol* 2014; **28**:1701–6.
46 Lora V, Bonaguri C, Gisondi P *et al*. Autoantibody induction and adipokine levels in patients with psoriasis treated with infliximab. *Immunol Res* 2013; **56**:382–9.
47 Gisondi P, Lora V, Bonauguri C *et al*. Serum chemerin is increased in patients with chronic plaque psoriasis and normalizes following treatment with infliximab. *Br J Dermatol* 2013; **168**:749–55.
48 Wu JJ, Poon KY, Channual JC, Shen AY *et al*. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol* 2012; **148**:1244–50.
49 Wu JJ, Guérin A, Sundaram M *et al*. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-alpha inhibitors versus methotrexate. *J Am Acad Dermatol* 2017; **76**:81–90.
50 Wu JJ, Sundaram M, Cloutier M *et al*. The risk of cardiovascular events in psoriasis patients treated with tumor necrosis factor-α inhibitors versus phototherapy: an observational cohort study. *J Am Acad Dermatol* 2018; **79**:60–8.
51 Wu JJ, Joshi AA, Reddy SP *et al*. Anti-inflammatory therapy with tumour necrosis factor inhibitors is associated with reduced risk of major adverse cardiovascular events in psoriasis. *J Eur Acad Dermatol Venereol* 2018; **32**:1320–26.
52 Roubille C, Richer V, Starnino T *et al*. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; **74**:480–9.
53 Dey AK, Joshi AA, Chaturvedi A *et al*. Association between skin and aortic vascular inflammation in patients with psoriasis: a case-cohort study using positron emission tomography/computed tomography. *JAMA Cardiol* 2017; **2**:1013–18.
54 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**:1066–73.
55 Ahlehoff O, Skov L, Gislason G *et al*. Cardiovascular outcomes and systemic anti-inflammatory drugs in patients with severe psoriasis: 5-year follow-up of a Danish nationwide cohort. *J Eur Acad Dermatol Venereol* 2015; **29**:1128–34.
56 Bissonnette R, Harel F, Krueger JG *et al*. TNF-α antagonist and vascular inflammation in patients with psoriasis vulgaris: a randomized placebo-controlled study. *J Invest Dermatol* 2017; **137**:1638–45.
57 Mehta NN, Shin DB, Joshi AA *et al*. Effect of 2 psoriasis treatments on vascular inflammation and novel inflammatory cardiovascular biomarkers: a randomized placebo-controlled trial. *Circ Cardiovasc Imaging* 2018; **11**:e007394.
58 Kim BS, Lee WK, Pak K *et al*. Ustekinumab treatment is associated with decreased systemic and vascular inflammation in patients with moderate-to-severe psoriasis: Feasibility study using (18)F-fluorodeoxyglucose PET/CT. *J Am Acad Dermatol* 2019; **80**:1322–31.
59 Low AS, Symmons DP, Lunt M *et al*. Relationship between exposure to tumour necrosis factor inhibitor therapy and incidence and severity of myocardial infarction in patients with rheumatoid arthritis. *Ann Rheum Dis* 2017; **76**:654–60.
60 Tam LS, Kitas GD, González-Gay MA. Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis? *Rheumatology (Oxford)* 2014; **53**:1108–19.
61 Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol* 2012; **26** (Suppl. 2):3–11.
62 Campanati A, Ganzetti G, Di Sario A *et al*. The effect of etanercept on hepatic fibrosis risk in patients with non-alcoholic fatty liver disease, metabolic syndrome, and psoriasis. *J Gastroenterol* 2013; **48**:839–46.
63 Boehncke S, Thaci D, Beschmann H *et al*. Psoriasis patients show signs of insulin resistance. *Br J Dermatol* 2007; **157**:1249–51.
64 Di Renzo L, Saraceno R, Schipani C *et al*. Prospective assessment of body weight and body composition changes in patients with psoriasis receiving anti-TNF-α treatment. *Dermatol Ther* 2011; **24**:446–51.
65 Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor-α therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. *J Eur Acad Dermatol Venereol* 2008; **22**:341–4.

66 Prignano F, Ricceri F, Pescitelli L *et al*. Comparison of body weight and clinical-parameter changes following the treatment of plaque psoriasis with biological therapies. *Curr Med Res Opin* 2009; **25**:2311–16.
67 Gisondi P, Conti A, Galdo G *et al*. Ustekinumab does not increase body mass index in patients with chronic plaque psoriasis: a prospective cohort study. *Br J Dermatol* 2013; **168**:1124–7.
68 Strober B, Leonardi C, Papp KA *et al*. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: etanercept comparisons and integrated data. *J Am Acad Dermatol* 2017; **76**:432–40.e17.
69 Savage L, Goodfield M, Horton L *et al*. Regression of peripheral subclinical enthesopathy in therapy-naive patients treated with ustekinumab for moderate-to-severe chronic plaque psoriasis. *Arthritis Rheumatol* 2018; **71**:626–31.
70 Lerman JB, Joshi AA, Chaturvedi A *et al*. Coronary plaque characterization in psoriasis reveals high-risk features that improve after treatment in a prospective observational study. *Circulation* 2017; **136**:263–76.
71 Martinez-Lopez A, Blasco-Morente G, Perez-Lopez I *et al*. Studying the effect of systemic and biological drugs on intima-media thickness in patients suffering from moderate and severe psoriasis. *J Eur Acad Dermatol Venereol* 2018; **32**:1492–8.
72 Ahlehoff O, Hansen PR, Gislason GH *et al*. Myocardial function and effects of biologic therapy in patients with severe psoriasis: a prospective echocardiographic study. *J Eur Acad Dermatol Venereol* 2016; **30**:819–23.
73 Pina T, Corrales A, Lopez-Mejias R *et al*. Anti-tumor necrosis factor-alpha therapy improves endothelial function and arterial stiffness in patients with moderate to severe psoriasis: a 6-month prospective study. *J Dermatol* 2016; **43**:1267–72.
74 Russo C, Jin Z, Elkind MS *et al*. Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. *Eur J Heart Fail* 2014; **16**:1301–9.
75 Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *JACC Cardiovasc Imaging* 2018; **11**:260–74.
76 Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol* 2009; **129**:1339–50.
77 Yeung H, Takeshita J, Mehta NN *et al*. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol* 2013; **149**:1173–9.
78 Khalid U, Hansen PR, Gislason GH *et al*. Psoriasis and new-onset diabetes: a Danish nationwide cohort study. *Diabetes Care* 2013; **36**:2402–7.
79 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.
80 Mease PJ, Gladman DD, Papp KA *et al*. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. *J Am Acad Dermatol* 2013; **69**:729–35.
81 Persson PG, Leijonmarck CE, Bernell O *et al*. Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993; **22**:268–72.
82 Armstrong AW, Voyles SV, Armstrong EJ *et al*. A tale of two plaques: convergent mechanisms of T-cell-mediated inflammation in psoriasis and atherosclerosis. *Exp Dermatol* 2011; **20**:544–9.
83 Tablazon IL, Al-Dabagh A, Davis SA, Feldman SR. Risk of cardiovascular disorders in psoriasis patients: current and future. *Am J Clin Dermatol* 2013; **14**:1–7.
84 Butcher MJ, Gjurich BN, Phillips T, Galkina EV. The IL-17A/IL-17RA axis plays a proatherogenic role via the regulation of aortic myeloid cell recruitment. *Circ Res* 2012; **110**:675–87.
85 Erbel C, Akhavanpoor M, Okuyucu D *et al*. IL-17A influences essential functions of the monocyte/macrophage lineage and is involved in advanced murine and human atherosclerosis. *J Immunol* 2014; **193**:4344–55.
86 Oikonomou E, Tousoulis D, Siasos G *et al*. The role of inflammation in heart failure: new therapeutic approaches. *Hellenic J Cardiol* 2011; **52**:30–40.
87 Fitzgerald R, Sadlier M, Connolly M, Tobin AM. Psoriasis and insulin resistance: a review. *J Diabetes Res Clin Metab* 2014; **3**:3.
88 Winer S, Paltser G, Chan Y *et al*. Obesity predisposes to Th17 bias. *Eur J Immunol* 2009; **39**:2629–35.
89 Toussirot E, Aubin F, Dumoulin G. Relationships between adipose tissue and psoriasis, with or without arthritis. *Front Immunol* 2014; **5**:368.
90 Endo Y, Asou HK, Matsugae N *et al*. Obesity drives Th17 cell differentiation by inducing the lipid metabolic kinase, ACC1. *Cell Rep* 2015; **12**:1042–55.
91 Wenk KS, Arrington KC, Ehrlich A. Psoriasis and non-alcoholic fatty liver disease. *J Eur Acad Dermatol Venereol* 2011; **25**:383–91.
92 Raychaudhuri SP, Raychaudhuri SK, Genovese MC. IL-17 receptor and its functional significance in psoriatic arthritis. *Mol Cell Biochem* 2012; **359**:419–29.
93 van Baarsen LG, Lebre MC, van der Coelen D *et al*. Heterogeneous expression pattern of interleukin 17A (IL-17A), IL-17F and their receptors in synovium of rheumatoid arthritis, psoriatic arthritis and osteoarthritis: possible explanation for nonresponse to anti-IL-17 therapy? *Arthritis Res Ther* 2014; **16**:426.
94 Raychaudhuri SK, Saxena A, Raychaudhuri SP. Role of IL-17 in the pathogenesis of psoriatic arthritis and axial spondyloarthritis. *Clin Rheumatol* 2015; **34**:1019–23.
95 Ruiz DG, Azevedo MN, Santos OL. Psoriatic arthritis: a clinical entity distinct from psoriasis? *Rev Bras Reumatol* 2012; **52**:630–8.
96 Ruutu M, Thomas G, Steck R *et al*. β-glucan triggers spondylarthritis and Crohn's disease-like ileitis in SKG mice. *Arthritis Rheum* 2012; **64**:2211–22.
97 Sherlock JP, Joyce-Shaikh B, Turner SP *et al*. IL-23 induces spondyloarthropathy by acting on ROR-γt^+ $CD3^+CD4^-CD8^-$ entheseal resident T cells. *Nat Med* 2012; **18**:1069–76.
98 Benham H, Rehaume LM, Hasnain SZ *et al*. Interleukin-23 mediates the intestinal response to microbial β-1,3-glucan and the development of spondyloarthritis pathology in SKG mice. *Arthritis Rheumatol* 2014; **66**:1755–67.
99 Gisondi P, Del Giglio M, Cozzi A, Girolomoni G. Psoriasis, the liver, and the gastrointestinal tract. *Dermatol Ther* 2010; **23**:155–9.