Psoriasis: Targets and Therapy

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REVIEW

Non-Alcoholic Fatty Liver Disease (NAFLD) in Patients with Psoriasis: A Review of the Hepatic Effects of Systemic Therapies

Deepak MW Balak[1,2]
Stefano Piaserico[3]
Ismail Kasujee[4]

[1]Department of Dermatology, LangeLand Ziekenhuis, Zoetermeer, the Netherlands; [2]Department of Dermatology, Ghent University Hospital, Ghent, Belgium; [3]Dermatology Unit, Department of Medicine, University of Padova, Padova, Italy; [4]Almirall GMA, Barcelona, Spain

Abstract: There is increasing interest in the association between psoriasis and non-alcoholic fatty liver disease (NAFLD), which is a prevalent liver disease characterized by excessive fat storage and inflammation that can progress to fibrosis and cancer. Patients with psoriasis have a two-fold higher risk to develop NAFLD and a higher risk to progress to more severe liver disease. Psoriasis and NAFLD share common risk factors such as smoking, alcohol consumption, and the presence of metabolic syndrome and its component disorders. In addition, both psoriasis and NAFLD hinge upon a systemic low-grade inflammation that can lead to a vicious cycle of progressive liver damage in NAFLD as well as worsening of the underlying psoriasis. Other important shared pathophysiological pathways include peripheral insulin resistance and oxidative stress. NAFLD should receive clinical awareness as important comorbidity in psoriasis. In this review, we assess the recent literature on the epidemiological and pathophysiological relationship of psoriasis and NAFLD, discuss the clinical implications of NAFLD in psoriasis patients, and summarize the hepatotoxic and hepatoprotective potential of systemic psoriasis therapies.

Keywords: non-alcoholic fatty liver disease, psoriasis, fumaric acid esters, Nrf2-activation

Introduction

Psoriasis is a chronic, immune-mediated inflammatory dermatological disease that affects nearly 150 million people worldwide. It is associated with a significant disease burden, a marked negative impact on patients' quality of life,[1] and places enormous pressure on health systems globally.[2–4] In recent years attention has focused on the inflammatory processes underpinning the pathophysiological changes in psoriasis. In particular, cutaneous inflammation in psoriasis is linked to chronic systemic low-grade inflammation, which is thought to underlie the associations of psoriasis with comorbidities such as psoriatic arthritis, mood disorders including depression, and a range of cardiometabolic disorders that include myocardial infarction, hypertension, obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), dyslipidemia, and hyperuricemia.[3,5]

One comorbidity of psoriasis that is increasingly recognized as clinically relevant is NAFLD.[3,6,7] NAFLD is characterized by excessive hepatic fat storage and is strongly associated with obesity, type 2 diabetes, and metabolic syndrome. Over time, NAFLD can progress to a more severe, inflammatory disease termed non-alcoholic steatohepatitis (NASH) and eventually to the development of cirrhosis.[8] NAFLD is the most common liver disease and its prevalence is rising rapidly. US

Correspondence: Deepak MW Balak
Email balak.dmw@gmail.com

Received: 6 October 2021
Accepted: 9 November 2021
Published: 7 December 2021

studies have reported a 10–35% prevalence in the general population with an average of between 20 and 30%.[9] The global prevalence of NAFLD is estimated to be 25%.[10,11] The presence of NASH in the general population is difficult to ascertain since it can be confirmed only by liver biopsy. However, rates between 1.5 and 6.5% have been reported.[9,10,12] NASH is a potentially progressive disease that can lead to cirrhosis in 12–25% of cases within a 10-year period, and it is associated with increased risks for hepatocellular carcinoma and cardiovascular- and liver-related deaths.[8,13,14]

NAFLD has been shown to occur 1.5 to 3 times more frequently in patients with psoriasis than in the general population.[3,11,15] Prevalences of NAFLD ranging up to 65% have been reported in this patient population.[16] The increased risk of NAFLD in psoriasis patients is not surprising, as the two diseases share a common link with the metabolic syndrome. However, there may be an association between psoriasis and NAFLD that is independent from the metabolic syndrome, hinging directly on the chronic low-grade systemic inflammatory burden characteristic of these two conditions.[5] Importantly, when psoriasis co-occurs with NAFLD the disease severity and morbidity of both conditions may be greater.[17]

The aim of this review is to evaluate the recent literature on the clinical and pathophysiological associations linking psoriasis with NAFLD, independently of the metabolic syndrome, focusing on the chronic low-grade inflammation underpinning the two disorders. Second, we aimed to assess the potential hepatotoxic and hepatoprotective effects of currently approved systemic psoriasis therapies, in particular dimethyl fumarate (DMF), an oral small molecule with pleiotropic effects that could positively impact NAFLD.

Search Strategy

For this narrative review, a targeted search of PubMed up to 14 July 2021 was conducted using the following search strategies: ‘psoriasis’ with (a) “non-alcoholic fatty liver disease/NAFLD” (n = 96), (b) “hepatotoxicity” 1/1/2010 to 14/7/2021 (n = 72), and (c) “hepatoprotection” (n = 14); “psoriasis treatment” with (a) “hepatotoxicity” 1/1/2010 to 14/7/2021 (n = 68), and (b) hepatoprotection (n = 11). Relevant papers were identified by reviewing abstracts or full papers (if required), and by contributory articles cited in the selected references. The bibliography was augmented by key articles known to the authors and, finally, by individual drug data identified via a search of LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK548744/).

Non-Alcoholic Fatty Liver Disease: Definitions and Spectrum

NAFLD is the most common chronic liver disease worldwide and, in the majority of patients, is strongly associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia. Individuals with metabolic syndrome have a 4- to 11-fold increased risk of developing NAFLD.[18] NAFLD is characterized by fat deposition in the liver, in the absence of viral diseases such as hepatitis B or C, significant alcohol consumption, use of steatosis-stimulating drugs such as methotrexate, steroids, amiodarone and tamoxifen, or certain hereditary conditions including Wilson’s disease and cholesteryl ester storage syndrome.[19,20]

NAFLD includes a wide spectrum of liver conditions with two main histological forms: simple hepatic steatosis (fat deposited, but no damage to liver cells) and NASH, which is characterized by hepatic inflammation that can lead to liver fibrosis. The aberrant pathophysiological processes underlying the progression to NASH are not fully understood, but are thought to include an imbalance of fatty acid metabolism leading to steatosis, and an elevated inflammatory response as a result of oxidative/metabolic stress and dysregulated cytokine production.[21] Potential consequences of these processes are the development of lobular hepatitis with perivenular/pericellular (chicken wire) fibrosis, NAFLD-associated cirrhosis and liver failure and, albeit infrequently, hepatocellular carcinoma (Figure 1).[5,22]

In terms of clinical presentation, the majority of NAFLD cases are either asymptomatic or have nonspecific symptoms such as fatigue and abdominal pain, and/or abnormal liver function test results. NAFLD can be diagnosed if > 5% hepatic steatosis is shown by liver ultrasound in the absence of excessive alcohol use.[8] The assessment for potential NASH requires additional testing using non-invasive assessment for liver fibrosis such as vibration-controlled transient elastography or magnetic resonance elastography. However, to confirm the diagnosis

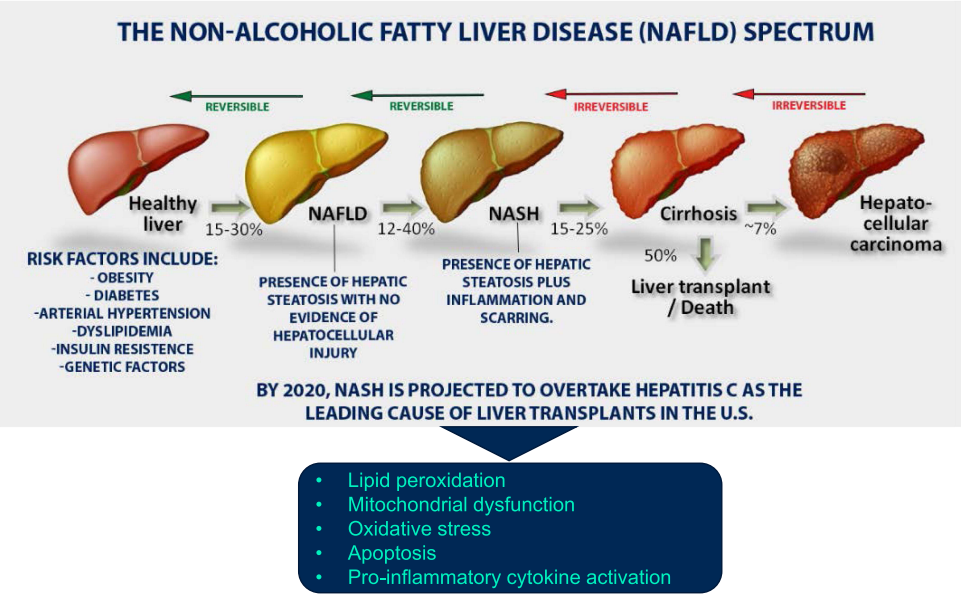

Figure 1 Spectrum of non-alcoholic fatty liver disease (NAFLD). Data from these studies.[5,22]

of NASH, histopathologic assessment of a liver biopsy is required.

Treatment of NAFLD is limited to optimal management of comorbid conditions such as type 2 diabetes and dyslipidemia, and lifestyle modifications aiming at 7–10% weight loss through caloric restriction and exercise.[8] Weight loss and increased physical activity/exercise can help normalize liver enzyme levels, reduce hepatic inflammation and improve insulin resistance, steatosis and liver histology.[23] There are currently no approved pharmacological therapies for NAFLD; oral vitamin E and pioglitazone are options that have shown modest clinical benefits.

Epidemiologic Links Between Psoriasis and NAFLD

The first published evidence in 2001 of a link between psoriasis and NAFLD involved three overweight/obese patients with NASH as confirmed by liver biopsy.[24] Since then, various observational and controlled studies have highlighted an increased prevalence of NAFLD in patients with psoriasis.[25–29] For example, in a large Dutch population-based study (2292 participants aged ≥ 55 years) the prevalence of NAFLD was 46% in 118 patients with psoriasis and 33% in individuals without psoriasis.[27] Importantly, while elderly study participants with psoriasis were 70% more likely to have NAFLD than those without psoriasis (crude odds ratio [OR] 1.70, 95% confidence interval [CI] 1.17–2.46), the increased risk was found to be independent of common risk factors such as smoking, alcohol consumption, and the presence of metabolic syndrome and its component disorders. A recent single-center cross-sectional study from Spain reported a 52% prevalence of NAFLD among a cohort of 71 patients with psoriasis.[15] Of note, 14% of patients had liver fibrosis as diagnosed with transitional vibration-controlled elastography. A large population-based cohort study, using UK data from 197,130 patients with psoriasis and 1,279,754 matched controls, reported an elevated risk for incident cases of NAFLD among psoriasis patients without systemic therapy (adjusted hazard ratio [HR] 1.18, 95% CI 1.07–1.30) and an even higher risk for those receiving systemic therapy (adjusted HR 2.23, 95% CI 1.73–2.87) compared with the control group.[30] The risk for incident NAFLD was also increased among patients with psoriatic arthritis, in particular for those receiving systemic therapy (adjusted HR 2.11, 95% CI 1.55–2.87). In line with these results, a 2015 systematic review and meta-analysis including 7 case-control studies found that patients with psoriasis had a 2-fold increased risk of NAFLD compared with controls (6 studies; n = 267,761; OR 2.15, 95% CI 1.57–2.94).[31] The risk of NAFLD was significantly greater in patients with psoriatic arthritis (3 studies; n = 505 patients; OR 2.25, 95% CI 1.37–3.71) and in patients with severe psoriasis (2 studies; 51,930 patients, OR 2.07, 95% CI 1.59–2.71) compared to those with mild psoriasis. Recently, this meta-analysis was updated to include 2 additional studies (for a total of > 3 million

patients and nearly 250,000 with NAFLD).[32] The analysis was extended to investigate potential risk factors for NAFLD in psoriasis patients which included hypertension, male sex, hyperglycemia and obesity. Reaffirming the findings of the original systematic review, there was a strong association between psoriasis and NAFLD independent of confounders.

In several studies, the presence and severity of psoriasis were associated with a higher prevalence and greater severity of NAFLD, and NAFLD was a strong predictor of higher Psoriasis Area and Severity Index (PASI) scores.[25,28,29,31,33] Using Control Attenuation Parameter to assess the degree of fatty liver and body surface area severity of psoriasis, Gandha et al confirmed a positive correlation between the two disorders.[34] Furthermore, the progression to more severe forms of liver disease appeared to be higher in patients with psoriasis.[35] Roberts et al reported that 48 of 103 (47%) psoriasis patients had NAFLD and 23 of 103 (22%) had biopsy-confirmed NASH, of whom 35% had stage 2–3 fibrosis.[35] The prevalence of NASH was markedly higher than the 12% previously reported in patients with similar demographic characteristics but without psoriasis in the same medical center. Moreover, concomitant NAFLD in patients with psoriasis may confer a higher 10-year cardiovascular risk compared to psoriasis patients without NAFLD.[36]

In summary, the epidemiologic association between NAFLD and psoriasis is particularly strong given the high prevalence and increased incidence observed among patients with psoriasis. Importantly, this association is more evident in patients with severe psoriasis compared with those with mild psoriasis and is independent of common traditional risk factors such as smoking, alcohol consumption, and the presence of metabolic syndrome and its component disorders.[5,31,32]

Pathophysiological Links Between Psoriasis and NAFLD

Psoriasis and NAFLD are amongst a number of multifactorial disorders (including cardiovascular diseases and metabolic syndrome) whose pathogenesis is not fully understood, but involves complex interactions between genetic, immunological and environmental factors (Figure 2).[5,37–42]

The pathophysiology of psoriasis is characterized by sustained, self-amplifying inflammatory responses that lead to uncontrolled keratinocyte proliferation and dysfunctional differentiation. Disturbances in both innate and adaptive cutaneous immune responses are responsible for psoriatic inflammation.[43] Activation of the innate immune system driven by endogenous signals and cytokines coexists with an auto-inflammatory response in some patients and with T cell-driven auto-immune reactions in others. Thus, psoriasis exhibits traits of an auto-immune disease on an auto-inflammatory background,[44,45] with both mechanisms overlapping and possibly potentiating one another. T helper (Th)-1, Th17 and Th22 cells and some of their associated pro-inflammatory cytokines, such as interleukin (IL)-17A and IL-22 and tumor necrosis factor alpha (TNF-α) are critically involved in sustaining and maintaining psoriasis.[45–48] The IL-23/IL-17 immune axis is considered to have a pivotal role in the pathogenesis of psoriasis; in line with this, IL-17- and IL-23-antagonists are highly effective treatments for psoriasis.[49,50]

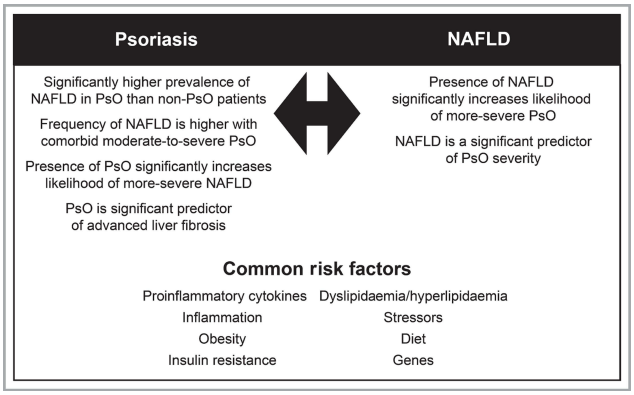

Figure 2 Common risk factors and associations between psoriasis (PsO) and non-alcoholic fatty liver disease (NAFLD). Reprinted from Prussick RB, Miele L. Non-alcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden? *Br J Dermatol.* 2018;179(1):16–29. © 2018 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.[5]

The pathogenesis of NAFLD is complex and involves multiple pathways. Important pathophysiological mechanisms include genetic factors, insulin resistance and hyperinsulinemia, oxidative stress and hepatocyte lipotoxicity, hepatic inflammation, fibrosis, and gastrointestinal dysbiosis.[21,38,51–55] The various factors are encompassed in a "multiple hit" model for NAFLD development and progression.[21,56] In the early stages of NAFLD, insulin resistance—possibly related to an increase in pro-inflammatory cytokines—plays a pivotal role by increasing the release of circulating free fatty acids, followed by abnormal accumulation of triglycerides in liver cells and hepatic steatosis. This may be followed by a phase in which

simple steatosis transitions into steatohepatitis as a result of an increased inflammatory response. Additional pathways subsequently involved in NAFLD progression include mitochondrial dysfunction and liver apoptosis, increased oxidative stress, activation of the profibrogenic transforming growth factor-β (TGF-β) pathway, and hepatic stellate cell activation and injury.[5]

While the exact underlying mechanisms must still be fully clarified, both psoriasis and NAFLD are strongly associated with low-grade, chronic inflammation, peripheral insulin resistance, and increased levels of oxidative stress.[40,57] Elevated insulin resistance and increased release of inflammatory cytokines are also characteristic of the metabolic syndrome and obesity. Adipose tissue produces adipocytokines (or adipokines) such as adiponectin, leptin and resistin, as well as pro-inflammatory cytokines which play important roles in the pathogenesis of both psoriasis and NAFLD.

Besides the important role of adipose tissue in mediating the interplay between skin and liver, (severe) psoriasis may have a direct impact on NAFLD, possibly via mechanisms beyond overweight and obesity. Indeed, NAFLD in the general population can also occur among individuals who are not obese and have a normal body mass index. These individuals are labelled as "lean" NAFLD.[58] Interestingly, compared to healthy subjects, individuals with "lean" NAFLD have higher mean serum C-reactive protein (CRP) levels, suggesting that systemic inflammation might be one of the pathogenic factors.[58]

The secretion of pro-inflammatory cytokines from psoriatic tissue into the general circulation may reinforce the prevailing systemic pro-inflammatory milieu associated with NAFLD. IL-6, IL-17, TNF-α and CRP produced by the liver (hepatokines) and psoriatic skin have reciprocal direct effects on these organs (Figure 3). The pro-inflammatory effects of adipocytokines and hepatokines are summarized in Table 1. Importantly, there may be a bi-directional relationship between psoriasis and NAFLD through pro-inflammatory pathways, postulated as the hepato-dermal axis.[48] Circulating pro-inflammatory cytokines such as TNF-α and IL-17 derived from psoriatic skin, upon reaching the liver, could impact liver inflammation and insulin resistance. Conversely, pro-inflammatory mediators stemming from hepatic inflammation could contribute to the onset or exacerbation of cutaneous inflammation in psoriasis. Pro-inflammatory immune modulators released by adipose tissue and the liver are involved in the

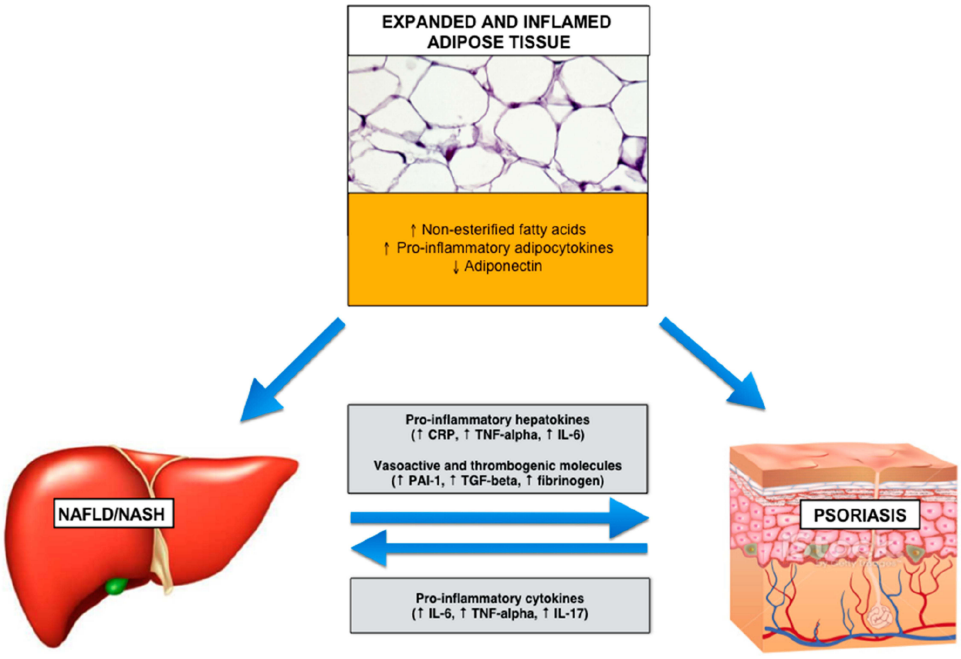

Figure 3 Possible mechanisms linking dysfunctional visceral adipose tissue, psoriatic skin and steatosis.
Notes: Reproduced from Mantovani A, Gisondi P, Lonardo A, et al. Relationship between non-alcoholic fatty liver disease and psoriasis: a novel hepato-dermal axis? *Int J Mol Sci.* 2016;17(2):217.[48]
Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; IL-17, interleukin-17; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PAI-1, plasminogen activator inhibitor-1; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor alpha.

Table 1 Cytokine Levels and Effects of Adipocytokines and Hepatokines in Psoriasis and Non-Alcoholic Fatty Liver Disease (NAFLD)

Cytokine Level in Psoriasis and NAFLD	Effect	
	Psoriasis	**NAFLD**
Pro-inflammatory adipocytokines levels (↑, increased; ↓, decreased)	**Role (↑, increases activity; ↓, decreases activity)**	
TNF-α ↑	↑ Keratinocyte proliferation, pro-inflammatory cytokines, angiogenesis	↑ Hepatic fibrogenesis: contributes to insulin resistance
IL-1 ↑	↑ Keratinocyte proliferation, adhesion molecule expression, pro-inflammatory cytokines	Activation of mitogen-activated protein (MAP) and ergosterol pathways
IL-6 ↑	↑ Keratinocyte proliferation	Contributes to insulin resistance
Leptin ↑	↑ Keratinocyte proliferation, Th1 response, angiogenesis	↑ Leptin resistance: contributes to hepatic fibrogenesis
Resistin ↑	↑ Pro-inflammatory cytokines	↑ Insulin resistance
Visfatin ↑		Contributes to insulin resistance
Ghrelin ↑		Negatively correlated to TNF-α
Anti-inflammatory adipocytokines		
Adiponectin ↓	↓ Anti-inflammatory cytokines	↓ Insulin sensitivity
Pro-inflammatory hepatokines		
Fibroblast growth factor 21 (FGF21) ↑ *	—	
Fetuin A ↑		
CRP ↑		↑ Hepatic fibrogenesis
TNF-α ↑		
IL-6 ↑		↑ Hepatic fibrogenesis

Notes: *NAFLD only. ↑, elevated, ↓ de-elevated. Adapted from Prussick RB, Miele L. Non-alcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden? *Br J Dermatol*. 2018;179(1):16–29. © 2018 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.[5]

Abbreviations: CRP, C-reactive protein; IL, interleukin; TNF-α, tumour-necrosis factor alpha.

promotion of hepatic fibrogenesis in NAFLD as well as psoriasis pathogenesis.[5,40,48,59] TNF-α, for example, is involved in psoriasis inflammation and has been shown to be an independent predictor of hepatic fibrogenesis and disease progression.[60] Another relevant cytokine in this context is IL-17, which plays a central role in psoriasis pathogenesis. IL-17 is able to induce hepatic stellate cells activation and subsequent collagen production.[50,61] By doing so, IL-17 facilitates the progression from simple liver steatosis to steatohepatitis.[50,61,62]

High circulating (or hepatic) levels of proprotein convertase subtilisin kexin type-9 (PCSK9) have been shown to play a key role in muscle and liver lipid storage, adipose energy storage and hepatic fatty acids and triglycerides storage and secretion. These effects contribute to involvement of the enzyme in the pathogenesis of both NAFLD[63] and psoriasis.[64]

Other shared pathways between psoriasis and NAFLD include modulation of lipid and glucose metabolism, which both play an important role in the development of metabolic syndrome and keratinocyte proliferation in psoriasis.

In summary, there is significant overlap in the pathophysiological factors underlying psoriasis and NAFLD, mostly relating to pathways involving inflammation, oxidative stress, and glucose and lipid metabolism.

Hepatic Effects of Systemic Psoriasis Treatments

Given the strong pathophysiological links between psoriasis and NAFLD and the high prevalence of NAFLD

among psoriasis patients, dermatologists should always screen for possible liver disease in their psoriasis patients. A good understanding of the potential hepatic effects of systemic treatments prescribed for patients with psoriasis would also be clinically important. NAFLD-promoting drugs should be avoided, especially in high-risk patients. On the other hand, systemic therapies that reduce systemic inflammation may have a positive influence and mitigate the risk of developing NAFLD. Below, we summarize hepatotoxic and potential hepatoprotective effects of currently approved systemic psoriasis therapies with a focus on NAFLD.

Hepatotoxic Effects of Systemic Psoriasis Treatment

Hepatotoxic risk is associated with the administration of a number of conventional drugs used in the treatment of psoriasis. Evidence for currently approved systemic psoriasis treatments is presented in Table 2.[65–87] Patients prescribed these medications should be monitored carefully for hepatotoxicity.

Perhaps the most substantive evidence, and concern, regarding potential hepatotoxicity relates to methotrexate.[65–70] Early signs of negative effects of methotrexate on liver function include elevated hepatic

Table 2 Potential Hepatotoxic Effects of Some of the Most Commonly Used Systemic Therapies Used in the Treatment of Moderate to Severe Psoriasis

Systemic Antipsoriatic Agent	Pharmacological Class	Potential Hepatotoxic Effects	Likely Causality[a]
Non-biological agents			
Acitretin (ACI)	Retinoid	Transient ↑AMT levels in up to 30% pts; rare acute toxic hepatitis; uncommon acute liver injury has been reported	ACI is a probable cause of clinically apparent liver injury
Apremilast (APR)	PD-4 inhibitor	No reported hepatotoxicity	APR is an unlikely cause of apparent liver injury, but clinical experience is limited
Cyclosporin (CYC)	Calcineurin inhibitor	Mild ↑ in bilirubin and less commonly AMT levels; case reports of acute liver injury have been reported	CYC is a probable rare cause of clinically apparent liver injury
Dimethyl fumarate (DMF)	Immunomodulator and anti-inflammatory	↑AMT levels which were asymptomatic and transient; isolated cases of clinically apparent liver injury with jaundice have been reported during widescale use of DMF	DMF is a probable rare cause of clinically apparent liver injury
Methotrexate (MTX)	Folic acid antagonist	During long-term low-dose MTX treatment ↑AMT levels; NAFLD, liver fibrosis and cirrhosis; with higher doses of MTX the increases in AMT levels are greater	MTX is a well-known cause of clinically significant hepatic injury, portal hypertension and cirrhosis
Biological agents			
Adalimumab (ADA)	Anti-TNFα	Low risk of transient, mild, asymptomatic ↑AMT levels; acute DILI (including AIH); cholestasis; reactivation of hepatitis B	ADA is a likely cause of clinically apparent liver injury
Certolizumab (CER)	Anti-TNFα	Low risk of transient, mild, asymptomatic ↑AMT levels; acute DILI (including AIH); cholestasis; reactivation of hepatitis B	CER is an unproven but suspected cause of apparent liver injury
Etanercept (ETA)	Anti-TNFα	Low risk of transient, mild, asymptomatic ↑AMT levels; acute DILI (including AIH), but much less than INF; cholestasis; reactivation of hepatitis B	ETA is a highly likely cause of clinically apparent liver injury
Infliximab (INF)	Anti-TNFα	Risk of transient, mild, asymptomatic ↑AMT levels, but sometimes the ↑ continues to progress; ↑ ALP; symptomatic hepatitis; acute DILI (including AIH); cholestasis; reactivation of hepatitis B	INF is a highly likely cause of clinically apparent liver injury

(*Continued*)

Table 2 (Continued).

Systemic Antipsoriatic Agent	Pharmacological Class	Potential Hepatotoxic Effects	Likely Causality[a]
Ustekinumab (UST)	Anti-IL12 and anti-IL23	No evidence of liver enzyme anomalies or reports of liver injury with UST to date. Rare instances of reactivation of hepatitis B have been reported. Experience with UST is limited	UST is an unproven but suspected rare cause of apparent liver injury and reactivation of hepatitis B
Brodalumab (BRO)	Anti-IL17	No evidence of liver enzyme anomalies or reports of liver injury with BRO to date. Experience with BRO is limited	BRO is an unlikely cause of apparent liver injury
Ixekizumab (IXE)	Anti-IL17	No evidence of liver enzyme anomalies or reports of liver injury with IXE to date. Experience with IXE is limited	IXE is an unlikely cause of clinically apparent liver injury
Secukinumab (SEC)	Anti-IL17	No evidence of liver enzyme anomalies or reports of liver injury with SEC to date	SEC is an unlikely cause of apparent liver injury
Guselkumab (GUS)	Ant-IL23	Mild-to-moderate ↑AMT levels which resolved even if treatment with GUS was continued. No evidence of acute liver injury, or reactivation of hepatitis B or worsening of hepatitis C with GUS to date, but clinical experience is limited	GUS is an unproven but suspected rare cause of apparent liver injury
Risankizumab (RIS)	Anti-IL23	Risankizumab has been associated with a low rate of serum aminotransferase elevations during therapy, but has not been linked to instances of clinically apparent liver injury.	RIS is an unlikely cause of apparent liver injury
Tildrakizumab (TIL)	Anti-IL23	No evidence of liver enzyme anomalies or reports of liver injury, or reactivation of hepatitis B or worsening of hepatitis C with TIL to date, but clinical experience is limited	TIL is an unlikely cause of apparent liver injury

Notes: [a]Based on LiverTox ratings.[76] Data from these studies.[65–87]
Abbreviations: ↑, elevated; AIH, autoimmune hepatitis; ALP, serum alkaline phosphatase; AMT, aminotransferase; DILI, drug induced liver injury; IL, interleukin; NAFLD, non-alcoholic fatty liver disease; TNF, tumor necrosis factor.

transaminase levels, but of even greater concern are methotrexate-induced histological changes including aggravation of underlying fatty liver to NAFLD and steatohepatitis with possible fibrosis and cirrhosis.[71,72] These more serious adverse hepatic effects have been reported to occur in about 5% of patients treated with chronic, low-dose methotrexate, although rarely in patients without additional clinical risk factors for hepatotoxicity, such as pre-existing liver disease, excessive alcohol abuse, hepatitis B or C, central obesity and type 2 diabetes.[71] Given the hepatotoxic concerns, use of methotrexate is preferably avoided in these high-risk psoriasis patient groups, including those with established NAFLD, and methotrexate is contraindicated if bilirubin values are > 5 mg/dl.[73]

Cyclosporin may cause dose-dependent, reversible increases in serum bilirubin and liver enzymes, with post-marketing experience reporting hepatotoxicity and liver injury.[65,68,74] Cyclosporin can also potentially worsen NAFLD by increasing serum lipid levels.[75] Close monitoring of liver function test enzymes and lipid parameters is recommended as abnormal values may necessitate dose reductions.[68,74,76] Another frequently occurring adverse event associated with cyclosporin use is hypertension, which would be expected to negatively impact NAFLD.

Cases of liver enzyme increases (≥ 3 upper limit of normal [ULN]) and elevation of total bilirubin levels (≥ 2 ULN) have been reported infrequently for dimethyl fumarate (DMF), with resolution after treatment discontinuation. Assessment of serum aminotransferases (eg, alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and total bilirubin levels are recommended prior to treatment initiation and during treatment.[68,77] DMF is considered to be a possible rare cause of liver toxicity.[78]

Acitretin has been associated with transient increases in liver enzymes, but hepatotoxicity has been reported rarely.[65] As acitretin frequently causes hyperlipidemia, use is preferably avoided in patients with or at high risk of NAFLD.[11,75,79,80]

No hepatotoxic effects have been documented for apremilast[65] and no routine laboratory monitoring is required. Apremilast is considered to be an unlikely cause of apparent liver injury.[78]

There is evidence of hepatotoxic risk with TNF-α inhibitors such as infliximab, adalimumab, certolizumab and etanercept[65,81–83] and guidelines advocate monitoring liver enzymes during treatment.[65] Furthermore, compared with conventional systemic therapies for psoriasis (methotrexate and cyclosporin), treatment with TNF inhibitors (adalimumab, infliximab and etanercept) was found to be associated with significant increases in bodyweight and body mass index in a network meta-analysis (6 studies and 862 psoriasis patients).[84] Increases in body weight might be associated with a reduction in the therapeutic response and/or exacerbations of comorbidities, although this needs to be confirmed in prospective studies. TNF inhibitors should be used cautiously in patients with or at high risk of NAFLD.

Other biologicals such as anti-IL17 agents (brodalumab, ixekizumab and secukinumab) and ustekinumab (anti-IL12/23) have been less widely investigated, but have generally exhibited minimal hepatotoxicity (Table 2). A retrospective study of 44 psoriasis patients receiving ustekinumab identified 6 cases (13.6%) of mild elevated transaminases, with no cases of severe hypertransaminasemia.[85] Overall, the reported rate of mild-to-moderate serum aminotransferase elevations following ustekinumab therapy was 0.5% to 1.4%. There have been no reports of treatment-related symptomatic acute liver injury or jaundice linked to ustekinumab therapy.[78] Interestingly, limited data found no increases in bodyweight in patients treated with ustekinumab.[84,88]

Analysis of over 3000 patients in clinical trials of the IL-17 antagonist secukinumab in psoriasis showed low rates of serum liver enzyme elevations compared to placebo and no cases of treatment-related liver injury. Post-marketing data have revealed no reports of liver injury due to secukinumab therapy.[78] Similarly, clinical trials (> 3000 patients) and post-marketing studies of the anti-IL-17 biologic brodalumab have shown no evidence of liver enzyme elevation nor liver injury attributable to the agent.[78] Comparable rates of serum liver enzyme elevations with the IL-17 antagonist ixekizumab and placebo were found in clinical trials, with no treatment-related cases of liver injury. Although post-marketing approval experience with ixekizumab is relatively limited, no cases of treatment-related liver injury have been reported.[78] For newer anti-IL-23 biologics recently approved for the treatment of psoriasis (eg, guselkumab, risankizumab, and tildrakizumab), no evidence of acute liver injury or reactivation of hepatitis B or worsening of hepatitis C has been reported to date, but clinical experience with these agents is very limited (Table 2).

Hepatoprotective Effects of Systemic Psoriasis Treatment

Assessment of hepatoprotection can be derived from several different research pathways including in vitro experiments, animal models and monitoring of potential biomarkers (Table 3).[89–108] Given the common etiology of inflammation between psoriasis and NAFLD, it might be postulated that systemic therapies for psoriasis that attenuate systemic inflammation may also have beneficial effects on NAFLD by targeting pro-inflammatory cytokines.[109] However, to date, clinical data are scarce for any direct hepatoprotective effects of systemic psoriasis treatments.

Methotrexate

Methotrexate has exhibited beneficial effects on cardiovascular inflammation[91,92] as well as decreasing serum levels of PCSK9, which is a likely marker of improved lipid metabolism (Table 3).[89] However, a large placebo-controlled RCT failed to show any benefits of methotrexate on the risk of cardiovascular events.[110] Furthermore, the potential hepatotoxic risks associated with methotrexate therapy, as discussed earlier, would generally preclude its use in patients with NAFLD.

Acitretin

From the clinical study of Krahel et al,[89] acitretin treatment was shown to increase PCSK9 levels, but there was no correlation between these elevated levels and markers of liver function such as transaminases in hepatic steatosis and NASH in high-risk patients (Table 3). Fibroblast growth factors (FGFs) 21 and 23 are markers for cardiometabolic disorders which are common in psoriasis. In one small trial, acitretin was reported to decrease FGF-21 by three-fold which was significantly greater than the reduction observed with methotrexate.[90] In an earlier small clinical trial, it was shown that patients with chronic psoriasis treated with acitretin had reduced retinol-binding protein-4 levels and decreased insulin resistance.[111] Given the link between psoriasis and increased insulin resistance/

Table 3 Potential Hepatoprotective Effects of Medicines Used to Treat Psoriasis

Treatment and Assessment	Results and Conclusions	Ref.
Effects on inflammatory biomarkers: non-biological agents		
MTX and ACI PCSK9 plays a role in maintaining lipid homeostasis by binding to LDL-R and is considered a cardiometabolic risk factor. Effects of MTX and ACI on PCSK9 levels in PSO pts and healthy volunteers after 12 weeks' treatment	PSO pts had significantly elevated PCSK9 levels compared with controls and these were positively correlated to BMI and TG levels. MTX, but not ACI, significantly reduced PCSK9 levels. However, there was no correlation between PCSK9 levels and markers of liver function such as transaminases in hepatic steatosis and NASH in high-risk patients	[89]
MTX and ACI FGFs 21 and 23 are markers for cardiometabolic disorders which are common in PSO. Effects of MTX and ACI on FGF-21 and −23 in PSO pts and healthy controls after 12 weeks' treatment	FGF-21 levels were increased in PSO pts vs controls whereas FGF-23 levels were not. There was a tendency for higher levels of FGF-21 in pts with more severe PSO which raises the possibility of its use as a biomarker for disease severity. Interestingly, ACI decreased FGF-21 more than MTX. Finally, there was a positive link between FGF-23 and AST levels which suggests a possible link with liver activity	[90]
MTX Review of the evidence for the potential pro-atherosclerotic effects of MTX	MTX improves endothelial function and vascular homeostasis, and is associated with a significant reduction in CV morbidity. These effects appear to be mediated via inhibition of pro-atherosclerotic cytokines such as TNF-α, IL-1 and IL-6	[91,92]
CYC TGFβs plays a key role in cell growth and differentiation, modulation of immune activity and regulation of the cell cycle. The effects of CYC on TGFβ levels was determined in PSO pts treated for 12 weeks	CYC significantly improved PSO symptoms and QoL of pts in this 3-month clinical study. CYC also increased the transcription activity of TGFβ1 at the end of treatment in pts with or without diabetes, and with or without metabolic syndrome	[93]
APR Assessment of efficacy, safety and metabolic biomarkers in 113 pts with PSO and/or PsA treated with APR for 1-year	Pts with diabetes treated with APR achieved better clinical benefit for their PSO (extent and severity) compared with non-diabetic patients. In addition, after 1 year, blood glucose levels and LDL-C levels were significantly reduced by APR	[94]
Effects on inflammatory biomarkers: biological agents		
ADA A 12-week RCT comparing the effects of ADA, PHO and PLA on vascular inflammation and markers of lipid and glucose metabolism, and inflammation in pts with moderate to severe PSO. This was followed by 52-week open-label ADA	ADA (anti-TNF) reduced key markers of inflammation including glycoprotein acetylation, CRP, IL-6 and TNF whereas PHO only reduced CRP and IL-6	[95]
ADA and FAEs The effect of ADA and FAEs on CV disease markers in pts with PSO was investigated in a 6-month RCT	ADA and FAEs were associated with beneficial CV effects. ADA significantly reduced systemic inflammation as measured by CRP levels and improved endothelial dysfunction as measured by flow-mediated dilation. In contrast, FAEs significantly reduced total cholesterol, LDL and apolipoprotein B levels	[96]
SEC A 12-week RCT comparing the effects of SEC and PLA on markers of inflammation, and lipid and glucose metabolism in pts with moderate to severe PSO. This was followed by 40-week open-label SEC	SEC (anti-IL-17A) was highly effective for treating PSO, but had a neutral effect on aortic vascular inflammation and biomarkers of cardiometabolic disease	[97]
SEC A post hoc analysis of 3 Phase III RCTs in pts with plaque PSO comparing SEC with PLA (and ETA in one study) with regards metabolic and liver parameters over 12 months	Overall, SEC had neutral effects on fasting plasma glucose, lipid parameters and liver enzymes. SEC reduced levels of CRP, a marker for systemic inflammation	[98]

(*Continued*)

Table 3 (Continued).

Treatment and Assessment	Results and Conclusions	Ref.
SEC or IXE (anti-IL-17A therapy) Determination of glucose levels in PSO pts to see if the severity of PSO was correlated with hyperglycemia, and to investigate the effects of anti-IL-17A therapy on glucose levels	In pts with PSO, the severity of the skin disease correlated with high blood glucose levels. Anti-IL-17A therapy significantly reduced glycemia in patients with PSO. In parallel experiments it had the same effect in imiquimod-treated mice (an animal model of psoriasis)	[99]
SEC The effects of SEC, CYC, and MTX on myocardial deformation and vascular function in PSO pts after 4- and 12-month treatment	In patients with psoriasis, inhibition of IL-17A with SEC produced greater improvement in arterial elasticity, coronary artery function and indices of myocardial deformation than either CYC or MTX. SEC was also associated with a reduction in markers for oxidative stress	[100]
UST A 12-week RCT comparing the effects of UST and PLA on markers of inflammation, and lipid and glucose metabolism in pts with moderate to severe PSO. This was followed by 40-week open-label UST	UST (anti-IL-12 and -IL-23) was highly effective for treating PSO and was associated with a reduction in IL-17a levels (a key cytokine in PSO). At the end of the study UST significantly decreased TNF-α, IL-1b, IL-17a and IL-6. VCAM-1 was significantly reduced by UST at 12 weeks, but this was not sustained at 52 weeks. Overall, UST transiently reduced aortic vascular inflammation at 12 weeks. Longer term UST produced a more durable reduction in markers (inflammatory cytokines) associated with CV disease	[101]
Effects in vitro		
Effect of DMF/MEF on GM-CSF- and IL-4-induced differentiation of monocyte derived DCs In vitro using human cell line	DMF concentration-dependently inhibited monocyte-derived DC differentiation as reflected by inhibition of CD1a, CD40, CD80, CD86 and HLA-DR, and reduced capacity to stimulate lymphocytes. This suggests that the mechanism of action of DMF/MEF in psoriasis is possibly based on immunomodulatory effects mediated through inhibition of DCs	[102]
Effect of DMF on DC maturation and subsequent T-cell responses In vitro using mouse cell line	DMF inhibited DC maturation by reducing inflammatory IL-12 and IL-6 production as well as expression of MHC class II, CD80 and CD86. This immature DC phenotype resulted in fewer activated T-cells (and decreased IFN-γ and IL-17 production). DMF modulates inflammation by inhibiting DC maturation and subsequent Th1 and Th17 cell differentiation	[103]
Animal models investigating possible hepatoprotective effects of systemic antipsoriatic medications		
To evaluate the antioxidant and anti-inflammatory effects of DMF as mechanisms for ameliorating liver toxicity Rat model of liver ischemia/ reperfusion injury	Liver histological tissue damage was significantly reduced by DMF and this was associated with lower ALT and MDA levels. In addition, DMF was associated with higher expression of anti-oxidant enzymes (catalase and glutamate-cysteine ligase modifier subunit) and lower levels of inflammatory mediators (nuclear factor-kappa B and cyclo-oxygenase-2). In a rat model of liver ischemia /injury, DMF significantly improved hepatic function and the anti-oxidant and inflammation status compared with controls (no treatment)	[104]
Effects on aerobic glycolysis in the modulation of immunity In vitro and in vivo experiments in mice and humans	DMF, an immunomodulatory drug, inactivated the catalytic cysteine of GAPDH involved in aerobic glycolysis in activated myeloid and lymphoid cells. Importantly DMF differentially impacted lymphocyte subsets, producing lymphopenia that selectively depleted highly glycolytic effector T-cells while sparing oxidative naïve T-cells and Treg cells. The anti-inflammatory/ immunomodulatory effects of DMF may be mediated via inhibition of GAPDH and aerobic glycolysis	[105]

(*Continued*)

Table 3 (Continued).

Treatment and Assessment	Results and Conclusions	Ref.
T-cell response to DMF Mouse model of EAE	$PLP_{139–151}$ peptide-reactive DMF-treated IL-17^{low}, IFN-γ^{low}, IL-4^{+} $CD4^{+}$ T-cells may protect mice from severe EAE. DMF-induced IL-17^{low}, IFN-γ^{low}, IL-4^{+} Th cells protect mice from severe EAE	[106]
Effect of DMF on hepatic injury Mouse model of ACT-induced hepatic injury	In this model DMF ameliorated ACT-induced liver injury primarily through anti-oxidant, anti-inflammatory and anti-apoptotic mechanisms in a Nrf-2-dependent manner. These results show that DMF can possibly be used for treating ACT-induced liver damage through targeting the Nrf-2/HO-1 pathway	[107]
Effect of DMF on hepatic injury Rat model of TAA-induced hepatic injury	DMF restored TAA-induced increased levels of ALT, AST, GGT, total bilirubin, uric acid, MDA, reduced glutathione. DMF also improved histopathological findings such as inflammatory cell infiltration, necrosis and bridging fibrosis. Markers of inflammation and oxidative stress were also significantly improved by DMF. DMF protects against TAA-induced hepatic damage via down-regulation of the inflammatory cascade and up-regulation of anti-oxidant mechanisms	[108]

Abbreviations: ACI, Acitretin; ACT, acetaminophen; ADA, adalimumab; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; DC, dendritic cells; DMF, dimethyl fumarate; EAE, experimental autoimmune encephalomyelitis; ETA, etanercept; FAEs, fumaric acid esters; FGF, fibroblast growth factors; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GGT, γ-glutamyl transferase; GM-CSF, granulocyte-macrophage-colony stimulating factor; HO-1, heme oxygenase-1; IL, interleukin; IXE, ixekizumab; LDL-R, low-density lipoprotein-receptor; MDA, malondialdehyde; MEF, monoethyl fumarate; MTX, methotrexate; Nrf-2/HO-1, nuclear factor erythroid-related factor-2; PHO, phototherapy; PLP, proteolipid protein; PCSK9, proprotein convertase subtilisin/kexin type 9; PSO, psoriasis; pts, patients; TAA, thioacetamide; TG, triglyceride.

diabetes these changes could be clinically meaningful if confirmed in a larger study.[111]

Cyclosporin

There is a paucity of data on the potential hepatoprotective effects of cyclosporin. In a small group of patients with moderate to severe psoriasis, comorbidity with diabetes or metabolic syndrome did not affect the efficacy of cyclosporin.[93] In another clinical study, cyclosporin significantly improved patients' psoriasis symptoms and this was associated with increased transcription activity of TGFβ1 at the end of treatment in those with or without diabetes, and with or without metabolic syndrome.[112] Through inhibition of the enzyme cyclophilin, cyclosporin has shown beneficial effects on liver fibrosis and cirrhosis in some patients. However, calcineurin-related toxicity has limited the possibility of long-term therapy and has required that dosages be kept low.[113]

Apremilast

Apremilast is a phosphodiesterase 4 inhibitor shown to be clinically effective in patients with psoriasis and/or psoriatic arthritis and also acts as a metabolic modulator. In individual cases, apremilast was shown to improve glucose metabolism[114] and lipid profile.[115] Similar findings were reported in a 1-year open observational study (Table 3).[94]

Fumaric Acid Esters Including Dimethyl Fumarate

DMF, and its active metabolite monomethylfumarate (MMF), are of particular interest in the context of this review due to their unique multiple mechanisms of action (Figure 4).[102,103,105,116,117] These include immunomodulatory and anti-inflammatory mechanisms that are potentially advantageous in psoriatic patients with comorbid NAFLD (Table 3). [116] For example, DMF/MMF regulates cellular responses to oxidative stress by modulating intracellular glutathione levels.[102] DMF/MMF also reduces oxidative stress through activation of Nrf2 (nuclear factor erythroid 2–related factor 2) which stimulates cytoprotective and anti-inflammatory factors such as HO-1 (heme oxygenase-1);-[103,106,116] and through inhibiting genes regulated by the transcription factor HIF-1α (hypoxia-inducible factor 1-alpha) and STAT3/STAT1 (signal transducer and activator of transcription) pathways.[116] MMF is an agonist for hydroxy-carboxylic acid receptor 2 (HCA2/ GPR109A [G protein-coupled receptor 109A]) which inhibits neutrophil adhesion and recruitment by COX-1 (cyclooxygenase 1) and PGE2

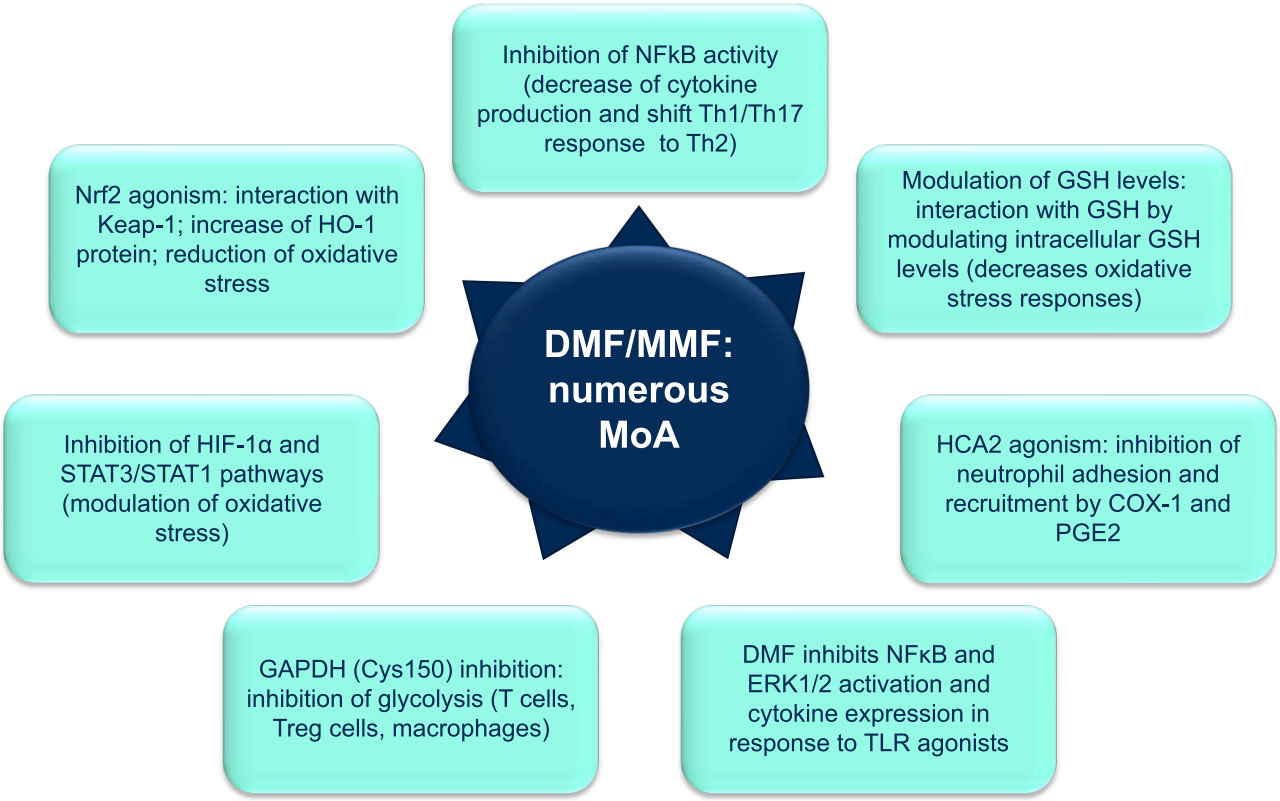

Figure 4 Proposed mechanisms of action of dimethyl fumarate/monomethyl fumarate (DMF/MMF).
Note: Data from these studies.[102,103,105,116,117]

(prostaglandin E2).[116] Fumaric acid esters significantly reduced total cholesterol, low-density lipoprotein and apolipoprotein B levels in a prospective trial involving psoriasis patients.[96] In animal models, DMF has shown potential to ameliorate acetaminophen-induced hepatic injury in mice,[107] as well as liver ischemia/reperfusion injury in rats.[104] Improvement of liver function and anti-oxidant status might prove to be a promising treatment approach in patients with psoriasis and comorbid NAFLD.

TNF Inhibitors

Adalimumab was shown to reduce key markers of systemic inflammation including glycoprotein acetylation, CRP, IL-6 and TNF and this was associated with beneficial cardiovascular effects such as improved endothelial dysfunction as measured by flow-mediated dilation.[95,96] TNF-α inhibitors have been reported to improve insulin resistance in patients with rheumatoid arthritis[118,119] and ankylosing spondylitis,[118,120] but not in obese patients with either type 2 diabetes[121] or metabolic syndrome.[122,123] Seitz et al investigated the impact of TNF-α inhibitors on the presence of liver fibrosis in patients with psoriatic arthritis and rheumatoid arthritis treated with methotrexate.[124] Patients with psoriatic arthritis had a higher incidence of liver steatosis and hyperlipidemia and in this study. TNF-α inhibitors exerted a protective effect against the development of liver fibrosis.

Secukinumab (Anti-IL-17)

Secukinumab has been shown to have neutral effects on fasting plasma glucose, lipid parameters and liver enzymes, while reducing levels of CRP, a marker for systemic inflammation. It was also associated with a reduction in markers of oxidative stress. Secukinumab produced greater improvement in arterial elasticity, coronary artery function and myocardial deformation indices compared with methotrexate and cyclosporin. However, no data are available on the impact of these effects on liver function.[97,98]

Ustekinumab (Anti-IL-12/23)

Ustekinumab significantly decreases pro-inflammatory cytokines, such as TNF-α, IL-1b, IL-17a and IL-6.

VCAM-1 was significantly reduced by ustekinumab at 12 weeks, although this effect was not sustained at 1 year. Overall, ustekinumab transiently reduced aortic vascular inflammation at 12 weeks and, longer term, produced a more durable reduction in inflammatory cytokines associated with cardiovascular disease.[101] No published studies have investigated the impact of this effect on liver inflammation and function.

Conclusions

NAFLD is an increasingly prevalent and clinically important comorbidity occurring in up to 65% of patients with psoriasis. The occurrence of NAFLD in psoriasis can have significant morbidity and mortality potential. There are multiple pathophysiological pathways that link psoriasis with NAFLD, in particular systemic inflammation and insulin resistance. Reducing systemic inflammatory burden may provide an opportunity to reduce the progression or even ameliorate NAFLD.

A number of conventional drugs used in the treatment of psoriasis are associated with hepatotoxic risk. Most evidence relates to use of methotrexate which, along with other NAFLD-promoting drugs, is best avoided in psoriasis patients with clinical risk factors for hepatotoxicity or established NAFLD. Despite the expectation that systemic psoriasis treatments might reduce the progression of or even ameliorate NAFLD by targeting pro-inflammatory cytokines, clinical data for direct hepatoprotective effects of these therapies are relatively scarce. Through its pleiotropic mechanisms of action contributing to its anti-inflammatory activity, DMF may have additional hepatoprotective effects of possible advantage in psoriatic patients with NAFLD.

However, real-world data on the effects of DMF in patients with psoriasis and concomitant NAFLD is currently lacking, and further studies with DMF and other systemic psoriasis therapies in routine clinical practice would be needed to inform therapeutic decision-making strategies for psoriasis patients with NAFLD.with DMF and other systemic psoriasis therapies in routine clinical practice would be needed to inform therapeutic decision-making strategies for psoriasis patients with NAFLD.

Acknowledgments

The authors thank Dr Rob Furlong and Dr Steve Clissold on behalf of Content Ed Net, Spain for editorial support, which was sponsored by Almirall, Barcelona, Spain, and performed in line with Good Publishing Practice (GPP-3) guidelines.

Funding

This article was supported by an unrestricted educational grant from Almirall, Barcelona, Spain.

Disclosure

DMWB is a consultant/speaker for AbbVie, Almirall, Celgene, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, and Regeneron/Sanofi Genzyme. IK is an employee of Almirall, Barcelona, Spain. SP is a consultant/speaker for AbbVie, Almirall, Celgene, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, UCB, and Pfizer. The authors report no other conflicts of interest in this work.

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