Title

Psoriatic disease and non-alcoholic fatty liver disease shared pathogenesis review

Authors

Torosian, Kelly

Lal, Esha

Kavanaugh, Arthur

et al.

Publication Date

2023-04-01

DOI

10.1016/j.semarthrit.2023.152165

Peer reviewed

HHS Public Access

Author manuscript

Semin Arthritis Rheum. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

Semin Arthritis Rheum. 2023 April ; 59: 152165. doi:10.1016/j.semarthrit.2023.152165.

Psoriatic disease and non-alcoholic fatty liver disease shared pathogenesis review

Kelly Torosian[a,1], **Esha Lal**[a,1], **Arthur Kavanaugh**[b], **Rohit Loomba**[c,d,e], **Veeral Ajmera**[c,d,*], **Monica Guma**[b,f,g,*]

[a]Department of Medicine, School of Medicine, University of California, San Diego, 9500 Gilman Drive, San Diego, CA 92093, USA

[b]Department of Rheumatology, University of California, San Diego, 9500 Gilman Drive, San Diego, CA 92093, USA

[c]Division of Gastroenterology and Hepatology, University of California, San Diego, 9500 Gilman Drive, San Diego, CA 92093, USA

[d]NAFLD Research Center, Department of Medicine, University of California at San Diego, La Jolla, USA

[e]Division of Epidemiology, Department of Family and Preventative Medicine, University of California at San Diego, La Jolla, USA

[f]Department of Medicine, Autonomous University of Barcelona, Plaça Cívica, 08193 Bellaterra, Barcelona, Spain

[g]San Diego VA Healthcare Service, San Diego, CA, 92161, USA

Abstract

Psoriatic disease (PD) and non-alcoholic fatty liver disease (NAFLD) potentially share disease pathways given the numerous inflammatory pathways involved in both diseases and a higher prevalence of NAFLD in PD patients. Metabolic syndrome and obesity are a key link between the two diseases, but even when controlling for this, associations between both diseases are still seen. Therapeutics that impact metabolic or inflammatory pathways may be impactful in both PD and

*Corresponding authors. v1ajmera@health.ucsd.edu (V. Ajmera), mguma@health.ucsd.edu (M. Guma).

[1]These authors share co-authorship.

Disclosures/Conflicts of Interest

Dr. Loomba serves as a consultant or advisory board member for Anylam/Regeneron, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Inipharm, Intercept, Ionis, Janssen Inc., Merck, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Promethera, Sagimet, 89 bio, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Boehringer-Ingelheim, Bristol-Myers Squibb, Cirius, Eli Lilly and Company, Galectin Therapeutics, Galmed Pharmaceuticals, GE, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Pfizer, pH Pharma, and Siemens. He is also co-founder of Liponexus, Inc. Dr Guma serves as a consultant of SonomaBio, and has received grant support from Novartis, Pfizer, Gilead and Genetech. Dr Kavanaugh serves as a consultant of SonomaBio, and has received grant support from Novartis, and Pfizer. They had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

CRediT authorship contribution statement

Kelly Torosian: Investigation, Writing – original draft. **Esha Lai:** Investigation, Writing – original draft. **Arthur Kavanaugh:** Investigation, Validation, Writing – review & editing. **Rohit Loomba:** Investigation, Validation, Writing – review & editing. **Veeral Ajmera:** Conceptualization, Methodology, Supervision, Investigation, Validation, Writing – review & editing. **Monica Guma:** Conceptualization, Methodology, Supervision, Investigation, Validation, Writing – review & editing.

NAFLD. In this review, we describe common inflammatory pathways contributing to both PD and NAFLD and critically review the potential impact of treatments for and on both diseases.

Keywords

Psoriatic disease; Non-alcoholic fatty liver disease; Pathogenesis; Inflammatory pathways; Insulin resistance

Background

Psoriatic disease (PD) is defined as the spectrum of conditions associated with the immune-mediated diseases psoriasis (PsO) and psoriatic arthritis (PsA). The defining condition of psoriatic disease is psoriasis (PsO). Psoriasis is a heterogeneous inflammatory condition that often presents with scaly, erythematous plaques on the trunk, scalp, and extensor surfaces. PsA, another common manifestation of PD, is characterized by immune-mediated inflammation of the joints and enthuses [1]. Approximately one-third of patients in North America with PsO were found to have coexisting PsA [2]. PD has a significant burden of disease and affects more than 8 million individuals in the United States and approximately 2–3% of people worldwide [3].

PD is associated with a host of comorbid conditions including cardiovascular disease, mood disorders, and metabolic syndrome [4]. An association between PD and nonalcoholic fatty liver disease (NAFLD), which is the hepatic manifestation of metabolic syndrome, has also been noted. NAFLD is the most common chronic liver disease in the world and is diagnosed by the presence of pathologic hepatic steatosis (≥5%) on imaging or liver biopsy in individuals who consume little or no alcohol and are without any secondary causes of hepatic steatosis [5]. For a subset of individuals, primarily those with non-alcoholic steatohepatitis (NASH), NAFLD is a progressive illness that can lead to fibrosis, cirrhosis, and hepatocellular carcinoma [6].

Approximately 20% of individuals with NAFLD have NASH, and 20% of these individuals may develop cirrhosis typically over a 20 to 30 year period [7]. A meta-analysis published in 2022 found that patients with psoriasis had almost double the odds of having NAFLD compared to patients without psoriasis (95% CI [1.70–2.26]; $p<0.001$) [8]. In addition, psoriasis patients with NAFLD also exhibited more severe skin disease [8,9].

This association was initially seen in a UK cross-sectional study of 9035 patients with psoriasis that investigated major comorbidities of psoriasis and correlation of psoriasis severity with these comorbidities. Patients were classified as mild, moderate or severe based on the degree of body surface area affected. Psoriasis was associated with 1.4 times higher prevalence of fatty liver disease compared to age matched controls (95% CI [1.12–1.76]) and secondary analysis revealed higher prevalence of NAFLD in patients with more severe psoriasis. An additional control-matched study found the frequency of NAFLD greater in psoriasis patients compared to controls (47% vs 28%; $p<0.0001$) and additionally described a greater severity of psoriasis based on Psoriasis Area and Severity Index (PASI) score (14.2 vs 9.6; $p<0.01$) in psoriasis patients with NAFLD compared to those without NAFLD. In

multivariate regression analysis, this association was independent of age, gender, and BMI [10].

While some studies have described the prevalence of liver disease in patients with psoriasis, very few have included patients with PsA [258,259]. One performed a population-based study in The Health Improvement Network. This study described the prevalence of liver disease and cirrhosis increased in patients with PsA [258]. Of note, the prevalence of liver disease and cirrhosis increased in a stepwise fashion with increasing body surface area affected by psoriasis. Yet, this study did not include imaging or histologic validation of liver disease. The other group documented the prevalence of liver disease among a mixed population with psoriasis and PsA utilizing percutaneous liver biopsy [259]. The prevalence of NASH was 22% of patients and more than one-third of these patients had stage 2-3 fibrosis, but liver biopsy was conducted only in a subset of these patients.The prevalence of NAFLD and NASH.

The association between dis ease severity of PD and concomitant NAFLD, and the presence of common other comorbidities suggests that there may potentially be shared etiopathogenic factors. In this review, we describe common inflammatory pathways contributing to both PD and NAFLD. We critically review the potential impact of treatments for PD on NAFLD and treatments for NAFLD on PD. Finally, we provide additional insight into a personalized approach to managing patients who have both PD and NAFLD.

Shared pathogenesis for NAFLD and PD

PD is thought to be caused by immune system activation following an environmental stimulus (infection or trauma) in genetically susceptible individuals. Immune cells including macrophages, T cells, and neutrophils infiltrate the dermis and aberrantly produce cytokines which drive the uncontrolled keratinocyte proliferation and dysfunctional differentiation – two processes central to the pathogensis of PsO [11]. The pathogenesis of PsA is closely linked to PsO in that it also involves an aberrant immune response and dysregulated cytokine production.

NAFLD pathogenesis is driven in part by excess lipid accumulation in the liver. Increased lipid deposition relative to decreased lipid removal by lipoproteins such as VLDL play a role in lipid accumulation in the liver. Three pathways contribute to hepatic lipid accumulation – high dietary lipid intake, fatty acid release from adipose tissue, and de novo lipogenesis in the liver. Hepatocytes are injured by precursors of triglyceride metabolism, and in turn, these hepatocytes release factors that promote immune cell migration and cause further liver injury from cytokines [12]. NAFLD is also affected by environmental factors, elevated BMI, and predisposing genetic factors that can also alter lipid homeostasis [13].

Mantovani et al. hypothesized that PD patients with NAFLD have a higher level of baseline inflammation than those without NAFLD [14]. The source of this inflammation is due to the hepato-dermal axis of inflammation (with contributions from the skin, liver, and adipose tissue). Psoriatic patients with NAFLD exhibit not only more severe psoriasis but also higher levels of C-reactive protein, a marker of underlying inflammation, as compared to psoriatic

patients without NAFLD [15]. A higher prevalence of advanced liver fibrosis is noted in PsO patients, and they also exhibit an increased risk of developing advanced liver fibrosis even when controlling for confounders such as BMI, diabetes, and metabolic syndrome [16,17].

Insulin resistance

Insulin resistance is seen in both psoriasis and NAFLD, independent of obesity [18]. The proinflammatory cytokines including Tumor Necrosis Factor alpha (TNF-alpha), IL-6, IL-17, and IL-22 and growth hormones, are elevated in psoriasis and contribute to insulin resistance by impairing insulin signaling in the body [19]. Cytokines and TNF-alpha are recognized as playing a crucial role in insulin sensitivity and inflammation, and Boehncke et al. found that the severity of psoriasis was significantly associated with increased insulin resistance [20].

Adipokines

Obesity is an established risk factor for NAFLD, affecting 50–90% of all obese adults [21-23]. Psoriatic patients also exhibit a higher prevalence of obesity as compared to the general population [22]. Weight loss decreases the burden of psoriatic skin disease and increases responsiveness to treatment [17]. Recent studies have supported a key role of adipokines in the relationship between obesity, psoriasis, and NAFLD.

Adiponectin

Adiponectin, a hormone that promotes insulin sensitivity and fatty acid oxidation, is closely associated with psoriasis and NAFLD [24]. Adiponectin is produced by adipose tissue, but plasma levels of adiponectin are paradoxically decreased in obesity due to excess visceral fat. The exact mechanism of this is unknown but it is thought to be related to an additional inhibitor of adiponectin that is also secreted by excess adipose tissue [25,26]. Adiponectin also plays a role in the regulation of inflammation. Adiponectin inhibits the production and action of TNF-alpha and IL-6 [27,28]. Adiponectin has an inhibitory effect on the IL-17 pathway described in detail below that drives psoriasis (Fig. 1) [29].

Adiponectin has also been linked to the production of anti-inflammatory cytokines such as IL-10 [30]. Kyriakou et al. showed that patients with psoriasis had lower plasma adiponectin levels compared to patients without psoriasis [31]. The exact mechanism is unknown, but is thought to be due to excess visceral adiposity, further supporting the link between metabolic syndrome and psoriasis [31]. Additionally, moderate and severe forms of psoriasis are associated with progressively lower levels of adiponectin as compared to milder forms [32].

Given the role of adiponectin in promoting insulin sensitivity and decreasing inflammation, it has also been studied in association with NAFLD [33]. Patients with NAFLD were shown to have significantly lower plasma adiponectin levels as compared to control patients [34]. A prospective study conducted in 2012 showed that patients with lower baseline levels of adiponectin were more likely to develop NAFLD over the course of 7 years as compared to those with higher baseline levels [35]. Lower levels of adiponectin have also been significantly associated with NAFLD severity (diagnosed via liver biopsy) [34]. Given

its role in the pathogenesis of both diseases, adiponectin levels could act as a risk marker in both conditions and potential target for treatment.

Leptin

Leptin, an adipokine that has been closely linked to NAFLD and PD, is produced by fat cells and is increased in obese individuals. Leptin is best known for its role in appetite suppression, but it also plays a role in systemic inflammation by promoting the production of various proinflammatory cytokines including TNF-alpha and IL-6 (Fig. 1) [36-38]. Hammingma et al. hypothesized that the production of these cytokines contributes to the development of psoriasis [38].

Leptin has also been associated with keratinocyte proliferation—a hallmark of psoriasis [39]. At baseline, PsO patients have been shown to have significantly higher circulating leptin levels compared to control patients [40]. Moreover, studies have shown that higher leptin/leptin receptor expression is observed in patients with more severe psoriasis as compared to those with milder disease [41]. Leptin's association with psoriasis is maintained even after controlling for obesity which could suggest that there are additional sources of leptin outside of adipose tissue [40].

Leptin is also strongly associated with NAFLD. Leptin binds to its receptor in hepatocytes and results in the phosphorylation of JAK2 which increases the expression of suppressors of cytokine signaling (SOCS-3) that act as a negative feedback loop to inhibit leptin and insulin signaling (Fig. 1). Overexpression of SOCS-3 can lead to leptin resistance [13]. Hyperleptinemia is thought to contribute to NAFLD in two ways. First, it promotes insulin resistance through IL-6 and TNF-alpha and leads to decreased lipid oxidation as well as increased synthesis of triglycerides and fatty acids [42]. Leptin is also thought to potentially decrease binding capacity of insulin to its receptors on the liver and increase lipogenesis in the liver when it is at very high levels in the body [13].

Leptin also contributes to the progression of NAFLD to NASH by promoting inflammation (via production of TNF-alpha) and fibrosis. It is thought to increase the activity of fibrotic cells in the liver including stellate cells, Kupffer cells, and sinusoidal endothelial cells (Fig. 1) [43,44]. Increased severity of NAFLD (via both fibroscan and NAFLD fibrosis scores) is associated with higher levels of circulating leptin. This relationship was preserved even when controlling for race, age, and gender and was strongest in patients with classic NAFLD (BMI>30) [45].

Cytokines

Patients with PD and NAFLD have high levels of baseline inflammation. Adipose tissue, psoriatic skin lesions, and livers with NAFLD produce and release multiple pro-inflammatory cytokines [14]. In the following section, we will describe the role of several important cytokines in the shared pathogenesis and progression of PD and NAFLD. As described in Mantovani et al., while there appears to be a network of inflammation, all the contributors to the network (and the directionality of their contributions) are not completely

understood.[14] Both psoriatic skin lesions and livers with NAFLD release proinflammatory cytokines, thereby contributing to systemic inflammation [19,46,47].

TNF-alpha

TNF alpha is elevated in the skin and synovium of psoriatic disease patients and is a key cytokine in the innate immune response that drives PD. It works by driving the release of other cytokines including IL-1 and IL-6 and increasing production of adhesion molecules [48]. TNF-alpha, in turn, plays a role in insulin resistance because it activates pro-inflammatory networks that lead to impaired insulin signaling at the level of the insulin receptors on myocytes and adipocytes. This interaction is further elucidated by TNF-alpha inhibitors like infliximab and etanercept which have been shown to promote insulin sensitivity in patients with both PD and Type II Diabetes Mellitus [49,50].

TNF-alpha is also secreted by hepatocytes and Kupffer cells in the liver, as well as indirectly secreted by abdominal fat (Fig. 1) [51]. TNF-alpha promotes insulin resistance as well as hepatic steatosis and triglyceride accumulation in the liver [52]. Over time this can lead to liver injury and inflammation. TNF-alpha has also been shown to be involved with the progression of NAFLD to cirrhosis [53]. In a study of patients with NASH, those with a higher degree of liver fibrosis had higher circulating levels of TNF-alpha [54].

IL-17

IL-17 is important for the pathogenesis and progression of PD. PsO patients exhibit more IL-17A+ cells in skin lesion samples when compared to healthy controls [55]. Additionally, IL-17 mRNA levels in psoriatic lesions positively correlate with disease activity [56]. IL-17 produces downstream cytokines such as IL-36, IL-19, and IL-22 which promote epidermal hyperplasia and parakeratosis (Fig. 1) [57]. Additionally, IL-17 induces the expression of S100 and LCN2 – two genes important for PsO progression. Il-17 also upregulates chemokine ligand CCL20 and chemokine receptor CCR6 which work synergistically to recruit T cells into the skin further driving skin inflammation [55,57,58].

There is also an association between IL-17 and PsA. Synovial biopsies from patients with PsA show elevated expression of IL-17 compared to synovium obtained from healthy controls [59]. IL-17 receptor expression is increased in synoviocytes obtained from PsA patients [60]. IL-17 contributes to PsA by upregulating proinflammatory cytokines such as IL-6 and matrix metalloproteinases (MMP-3) which contribute to the inflammation and tissue remodeling [1,61,62]. In murine models of inflammatory arthritis (collagen-induced arthritis), IL-17A expression promotes osteoclast expansion and bone resorption [63]. IL-17 signaling also upregulates RANKL receptor expression [62].

IL-17 also plays an important role in the development of NAFLD. In human hepatic tissue, the extent of steatosis is positively correlated with the number of IL-17A+ cells ($R = 0.5425$; $p = 0.007$). Additionally, triglyceride levels within hepatocytes are positively correlated with IL-17A mRNA levels ($R = 0.2432$; $p = 0.0442$) [64]. Murine models of NAFLD and NASH have helped elucidate IL-17′s role in the disease. In mice on a high fat diet, IL-17 was shown to activate a c-Jun N-terminal kinases-dependent pathway that inhibits PPAR-alpha—an important regulator of fatty acid beta-oxidation. This is one potential

mechanism by which IL-17 promotes triglyceride accumulation in the liver. In the same model, treatment with recombinant IL-17 led to hepatic steatosis, oxidative liver damage, and aminotransferase elevations [65].

IL-17 may also play an important role in the development of NASH. Tang et al. demonstrated that IL-17 plays a role in the evolution of simple steatosis to steatohepatitis [66]. In the choline-deficient diet-induced (MCD) murine model for NASH, IL-17A activates JNK-1– a MAPKinase involved in hepatic fibrosis and lipoapoptosis [67-69]. IL-17A also promotes fibrosis by upregulating the expression of the TGF-Beta receptor (profibrotic cytokine) on hepatic stellate cells (Fig. 1) [70]. IL-17 also plays a role in inflammatory cell recruitment to the liver. Tang et al. showed that IL-17 blockade after inducing systemic and hepatic inflammation in the mice with lipopolysaccharide (LPS) injection decreased inflammatory cells in the liver [66]. IL-17 knockout in MCD mice resulted in markedly decreased lobular inflammation compared to the WT [68].

IL-22

IL-22 has also been closely associated with PD. Biopsies obtained from psoriatic skin lesions contain higher levels of IL-22 compared to biopsies obtained from healthy controls [71]. Plasma levels of IL-22 are upregulated in PsO patients and positively correlated with PsO disease severity [71]. IL-22 upregulates multiple genes involved in the migration of keratinocytes and downregulates the differentiation of keratinocytes through signaling molecules [71]. IL-22 treatment of in vitro models of human skin resulted in parakeratosis, acanthosis, and epidermal hyperplasia – further histological evidence of the impaired differentiation (Fig. 1) [72,73].

The role of IL-22 in the pathogensis of PsA is unclear.. Mitra et al. showed increased levels of IL-22 in synovial fluid samples obtained from PsA patients as compared to samples obtained from OA patients [60]. Additionally, treatment of fibroblast-like synoviocytes (FLS) obtained from patients with PsA with recombinant IL-22 resulted in significantly increased proliferation. Blockade of the IL-22R with a monoclonal antibody inhibited the FLS proliferation suggesting a potential role of IL-22 in pannus formation. Although IL-22 has been identified in synovial fluid in patients with PsA, it has not been identified in synovial tissue samples [74]. Moreover, studies in mouse models of immune-mediated arthritis have implicated Il-23 (through its actions on the $\gamma\delta$ T cells) as the primary driver of joint inflammation, bony erosions, and entheseal inflammation. This suggest that PsA arthropathy develops independently of IL-22 [63,75-77].

IL-22 has been shown to have mixed effects on the liver. IL-22 promotes the production of multiple acute phase reactants in the liver including serum amyloid A and fibrinogen [78]. IL-22 also recruits fibrosis-promoting Th17 cells to the liver through its effect on CCL20 [68]. On the other hand, IL-22 has been shown to be hepatoprotective against liver injury in murine models of liver disease. IL-22 activates STAT3 which mediates multiple downstream anti-apoptotic genes such as MCl-1, Bcl-2, and Bcl-xL. IL-22 is also mitogenic, promoting the formation of c-Myc and cyclin D1 [79]. In a murine model of autoimmune hepatitis, neutralization of IL-22 antibodies led to significant increases in ALT and AST and significant necrosis of the liver. Conversely, ALT/AST elevations and necrosis were

markedly less when injection of recombinant IL-22 preceded liver injury [79]. Finally, IL-22 promotes the production of antioxidants like metallothionein 1 and 2, enhancing hepatic tissue regeneration [80].

IL-6

Psoriatic plaques in patients with PsO exhibit much higher levels of IL-6 as compared to samples obtained from healthy non-lesional skin. Patients with active PsO also exhibit elevated plasma levels of IL-6 than healthy controls [81,82]. Two potential sources for the elevated IL-6 have been proposed in patients with PsO – peripheral blood monocytes and keratinocytes [82,83]. IL-6 induces phosphorylation of STAT3 which leads to increased cell proliferation and the development of other histological features of PsO. IL-6 also plays a role in the IL-23/IL-17 pathway by inducing CD4+ T cells to differentiate into IL-17 producing Th17 cells (Fig. 1) [84].

IL-6 also contributes to the development of PsA. Synovial tissue analyses in patients with PsA show increased expression of IL-6 [85]. Patients with PsA have significantly higher plasma levels of IL-6 than control patients with OA [86]. Plasma levels also appear to correlate with disease activity including number of swollen and painful joints, ESR, and CRP levels [87]. IL-6 is thought to contribute to PsA by promoting synovitis, bone resorption, and cartilage degeneration as well as synovial hyperplasia, neovascularization, and infiltration of inflammatory cells into synovium [88].

In a study of 50 patients with NAFLD, researchers found increased IL-6 expression in livers of patients with NASH as compared to patients with only steatosis or normal controls. Furthermore, the severity of inflammation and stage of fibrosis was directly related to the hepatic expression of IL-6. Interestingly, these patients also had higher rates of insulin resistance suggesting another shared pathway between NAFLD and PD [89].

IL-23

IL-23 is a major driver of PD. Lesional skin biopsies in patients with PsO contain significantly higher levels of IL-23 p19 mRNA as compared to skin biopsies taken from lesion-free areas [90]. The IL-23 pathway works in conjunction with IL-17 in PD. Environmental stimuli (trauma or infection) and autoantigen presentation stimulate TNF-alpha production. TNF-alpha activates dendritic cells in the skin that produce IL-23 [57,91,92]. IL-23 promotes the production of IL-17 and IL-22 by activating Th-17 and Th-22 cells [57]. In PsA specifically, IL-23 activates Th-17 cells and triggers the STAT3 and RAR-related orphan receptor gamma signaling pathway responsible for producing IL-17A, IL-17F, and IL-23R [93]. Th17 cells also produce TNF, interferon gamma, and granulocyte macrophage colony-stimulating factor [94]. As outlined above, IL-17 and IL-22 play important roles in the pathogenesis of PsA and PsO.

IL-23 also plays a role in the development of NAFLD. IL-23 expression is upregulated in NAFLD patients compared to healthy controls. Similar to PD, IL-23 modulates the activation and differentiation of Th17 cells and production of IL-17. As described above, IL-17 plays a central role in the development of NAFLD and the progression from NAFLD to NASH (Fig. 1) [95].

PD and NAFLD treatments

Weight loss and diet

There are no medications currently approved to treat NAFLD, and the mainstay of treatment continues to be weight loss and lifestyle modifications [96-99]. Weight loss of 5% of total body weight can reduce hepatic steatosis, while losing up to 10% of body weight can reduce lobular inflammation, ballooning, and fibrosis on liver biopsy. Modest weight loss also improves systemic inflammation by reducing excess visceral fat and improving insulin resistance [96]. Vilar-Gomez et al. demonstrated a dose-response relationship between weight loss and histological changes in a prospective study of patients with NASH with 45% of patients with >10% of body weight loss showing biopsy proven regression of fibrosis [100].

Weight loss is also efficacious in the treatment of psoriatic diseases. A randomized control trial conducted by Jensen et al. showed that reduction in PASI scores was significantly correlated with weight loss in overweight patients with psoriasis [101]. The study also hypothesized that there may be a dose-response relationship because the greatest reductions in PASI scores occurred during the first phase of the study when participants lost the most weight [101]. In an RCT conducted in 2014, Naldi et al., showed that dietary intervention and increased physical activity led to weight loss and reduction in mean PASI scores in overweight and obese patients with moderate-to-severe plaque psoriasis [102]. Weight loss also improves responsiveness of patients with PsO to low-dose cyclosporine and anti-TNF therapy [17,103].

Multiple studies have also demonstrated the value of the Mediterranean diet in improving NAFLD.[104,105] A study of 12 non-diabetic patients with NAFLD found that when comparing the Mediterranean diet with a low fat/high carbohydrate diet, those on the Mediterranean diet showed a significant reduction in hepatic steatosis and improved insulin sensitivity. Interestingly, these patients did not have a significant reduction in weight, further exemplifying that there are likely inflammatory pathways in NAFLD that are independent of obesity [104]. Kontogianni et al. also studied the Mediterranean diet in NAFLD patients and found that those who were adherent to the diet had less severe liver disease and less insulin resistance [105]. The Mediterranean diet has also been studied in PD patients. A cross-sectional observational study conducted by Phan et al. showed that adherence to a prescribed Mediterranean diet was significantly and inversely related to psoriasis severity, but further studies should be done to determine if a causal relationship is present [106].

PD treatments in NAFLD

There have been significant advances in FDA approved therapeutics for PD over the last 20 years, most significant are those that target the aforementioned cytokine and adipokine pathways. TNF-alpha inhibitors (Infliximab, Adalimumab, Etanercept, Certolizumab, and Golilumab) are efficacious in the treatment of PD (PsO and PsA) and show promise in NAFLD and NASH (Table 1). Studies in rat and mouse models of NAFLD and NASH showed that treatment with infliximab reduces inflammation, steatosis, insulin resistance, and fibrosis induced by a high-fat diet [107-109]. In a rat model of NASH, treatment

with adalimumab improved histology and LFTs, although it did not protect against the development of NASH [110].

A cross-sectional study in 2010 showed that TNF-alpha inhibitors may protect against the development of fibrosis in patients with PsA [111]. This finding was reproduced by Campanati et al., 2013 who showed that etanercept decreased the odds of developing hepatic fibrosis in patients with PsO and NAFLD [112]. Although promising, additional studies on TNF-inhibitors in human subjects with both PD and NAFLD are needed to assess if they are able to treat both conditions simultaneously.

IL-17 blockade is also effective in treating PsO and PsA. A recent study in patients with active PsA and PsO showed that treatment with ixekizumab (IL-17A inhibitor) (IXE) led to symptom improvement (Table 1). Achievement of PASI 100 AND ACR 50 (scores to measure disease improvement) simultaneously was higher in patients treated with IXE compared to patients treated with adalimumab (ADA) (39.2% vs 26.1%; $p<0.001$), demonstrating that IXE is superior to ADA (TNF-alpha inhibitor) in simultaneously treating joint and skin symptoms[113].

The efficacy of IL-17 blockade has not been formally studied in patients with NAFLD. In mouse models of NAFLD and NASH, IL-17 blockade decreases hepatic steatosis and hepatic infiltration of inflammatory cells (Table 1) [39,68]. Although further studies are needed to evaluate if IL-17 blockade can effectively treat both NAFLD and PD, IL-17 is not hepatotoxic and likely safe to use in patients with PD and NAFLD. A recent study by Gerdes et al. showed that treatment with secukinumab (an IL-17A antagonist) in patients with PD promoted a small decrease in body weight and did not worsen AST and ALT levels[114].

Therapeutic administration of IL-22 has been explored in murine models only (Table 1). One study in a high-fat-diet-fed mice model of NAFLD showed that recombinant IL-22 improved insulin resistance and hepatic steatosis through its effect on a downstream lipid metabolism gene [115]. In mice homozygous for obesity mutation fed with a high-fat diet, recombinant IL-22 decreased triglyceride and cholesterol levels in the liver, as well as downregulated expression of genes important for lipogenesis [116]. Given IL-22′s hepatoprotective properties, recombinant IL-22 has been studied in human patients with other liver conditions. One phase 2 clinical trial showed recombinant IL-22 significantly decreased MELD scores, inflammatory markers, and aminotransferase levels and upregulated regenerative markers in patients with moderate to severe alcoholic hepatitis [117].

IL-17 blockade could also be a means of increasing endogenous levels of IL-22. Knockout of IL-17 in a mouse model of NAFLD increased the number of Th22 (IL-22 producing) cells. The presence of IL-17 attenuates the protective effects of IL-22 through inhibition of the PI3K-Akt signaling pathway. Therefore, IL-22 levels and cytoprotective efficacy may be increased through IL-17 blockade, but further research on this in human subjects is needed [68].

Although the therapeutic potential of IL-22 administration is promising, there are few clinical studies investigating its efficacy in PD. Phase 1 trials have shown recombinant

versions of IL-22 to be safe in humans [66,118]. In 2011, the phase 1 clinical study investigating the efficacy of a single dose ILV-095 on disease activity in patients with plaque PsO was terminated due to the inability to statistically evaluate its efficacy endpoints [119].

Medications targeting IL-23-mediated pathways have also been shown to be efficacious in the treatment of PD (Table 1). Currently, monoclonal antibodies targetting the p19 subunit of IL-23 (Tildrakizumab and Risankizumab) and the p40 subunit of IL-12 and IL-23 (Ustekinumab) are approved in the United States to treat both PsO and PsA. Although these medications have not been specifically studied in humans for the treatment of NAFLD and NASH, preliminary investigations in a mouse model showed that IL-23 blockade can prevent the development of NAFLD [120]. Treatment with ustekinumab in patients with PsO can lead to a significant reduction in levels of TNF-alpha, IL-17a, and IL-6 levels (Table 1) [121]. Ustekinumab has also been shown to be safe in patients with pre-existing liver disease and unlikely to cause liver injury likely [122]. Given that ustekinumab can decrease the levels of several cytokines important for the pathogenesis of NAFLD/NASH, it may be an effective treatment modality for both conditions but future investigations are needed.

IL-6 blockade studies have mixed results in PD. A RCT in 2016 showed that IL-6 blockade with clazukizumab in patients with active PsA and PsO led to statistically significant improvement in ACR20 on week 16 at the 100 mg dose [123]. Interestingly, ACR 20/50/70 scores in patients treated with either 25 mg or 200 mg doses of clazakizumab did not differ significantly when compared to placebo, indicating a lack of a dose-response to the drug (Table 1) [123]. A case series published in 2012 showed that treatment of PsA and PsO with tocilizumab for 6 months did not improve skin or joint symptoms [88]. Although IL-6 overexpression has been associated with PsA and demonstrated in synovial tissue samples, it may not play a central role in the pathogenesis of PsA synovitis [74]. This could explain why improvement in joint symptoms is not consistently demonstrated in PsA patients on IL-6 blockade [88].

IL-6 blockade in patients with PsO also has mixed results. Mease et al. showed that IL-6 blockade failed to improve skin symptoms in patients with active PsO and PsA and even worsened skin symptoms in one patient [123]. Interestingly, IL-6 blockade has been shown to induce PsO in select patients with rheumatoid arthritis [124,125]. One proposed theory for this is that IL-6 receptor blockade leads to a temporary elevation in serum IL-6 that stimulates other members of the IL-6 receptor family [126].

There is minimal data on the impact of IL-6 on NAFLD (Table 1). In the clazakizumab RCT trial described above, IL-6 blockade led to benign transaminase elevations. The highest dose (200 mg of clazakizumab) led to more patients with AST/ALT elevations more than three times the upper limit than any of the other dosages [123]. Until more research on the effect of IL-6 antagonism on the liver is done, IL-6 blockade should be used cautiously in patients with PD and NAFLD.

Apremilast, a phosphodiesterase-4 inhibitor, is another approved treatment for PsO and PsA (Table 1). Although apremilast has not been formally studied in NAFLD, it has been shown to modify important NAFLD risk factors in animal models of the disease.

Phosphodiesterases are thought to contribute to the development of NAFLD through enzymatic degradation of hepatoprotective cyclic adenosine monophosphate (cAMP). cAMP is a secondary messenger molecule that modules inflammation and lipid metabolism by modifying gene/protein expression [127]. In a mouse model of obesity, increasing cAMP levels (by inhibitoing phosphodiesterases) improved hepatic steatosis by inhibiting de novo lipogenesis and promoting mitochondrial biogenesis and fatty acid beta oxidation [128].

PDE4B knockout in mice decreased serum leptin and TNF-alpha levels, fat pad weights, and adipocyte size [129]. In rats, PDE4 inhibition upregulated GLP-1, an incretin important for glycemic control and weight loss [130]. Synthetic PDE4 inhibitors administered in multiple rodent models of hepatic disease resulted in decreases in aminotransferase levels, fibrosis scores, and histological evidence of inflammation [131].

Despite the promising findings in animal models, data from human studies show evidence of only NAFLD/NASH risk factor modification. In the PALACE-2 trial, a phase three randomized controlled trial, apremilast promoted weight loss in 15% of patients [132]. In Mazzili et al., 2020, apremilast administration decreased LDL-C and glucose levels in patients with PsO and PsA [133]. PDE4 inhibition seems to have little impact on disease markers of NASH/NAFLD in humans. ASP9831, a novel PDE4 inhibitor, did not improve any biochemical hepatic parameters in patients with a histological diagnosis of NASH [131]. PDE4-inhibition must be studied more carefully in humans before definitive conclusions regarding its efficacy in NAFLD/NASH can be drawn.

Abatacept, a cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4)–Ig human fusion protein, is an approved treatment for PsA, but has shown mixed effects on PsO (Table 1) [134]. Abatacept inhibits the CD-28 costimulatory signal needed to activate naive T cells. To date, no studies evaluating the potential use of abatacept in the treatment of NAFLD/NASH have been done. Preliminary studies in mice infected with *S. mansoni* cercariae showed CTLA4-Ig can attenuate fibrosis through suppression of pro-fibrotic genes and collagen deposition [135]. In a mouse model of graft versus host disease, CTLA4-Ig decreased colonic and lung fibrosis and transaminase elevations [136]. CTLA4-Ig could theoretically inhibit fibrosis– a key pathway in NASH, but specific studies evaluating Abatacept in models of NAFLD/NASH must be done.

Fumaric acid esters (FAE) including dimethyl fumurate (DMF) are approved to treat PsO, but have not yet been approved to treat PsA due to the paucity of supportive studies (Table 1) [137,138]. It is proposed that DMF and FAEs treat PsO by impairing keratinocyte proliferation and decreasing expression of vascular cell adhesion molecule 1 (VCAM-1), E-selectin, intercellular adhesion molecule 1 (ICAM-1), and IL-1 α [139-141].

Although FAEs have not been specifically studied in NAFLD/NASH, preliminary studies in other rodent models of hepatic injury are promising. In mouse and in vitro models of alcoholic liver disease, DMF decreased hepatic steatosis, hepatic immune cell infiltration, expression of multiple inflammatory cytokines, and production of reactive oxygen species [142,143]. In rat models of acetaminophen mediated hepatic injury and ischemia/reperfusion injury, DMF decreased hepatic injury and inflammation and increased levels of various

antioxidants [144,145]. Although FAEs are protective against hepatic injury in other rodent models of liver disease, studies on their impact on NAFLD/NASH are still needed [146].

NAFLD treatments in PD

The PIVENS trial compared treatment with Vitamin E, pioglitazone, and placebo in non-diabetic patients with NASH and found Vitamin E to be superior to both pioglitazone and placebo in improving steatohepatitis (43% vs. 19%; $p = 0.001$). Improvement in steatohepatitis with pioglitazone compared to placebo was 34% vs 19% ($p = 0.04$), and secondary endpoints of steatosis, inflammation and hepatocellular ballooning were significantly improved. Pioglitazone was associated with improvements in insulin resistance but caused weight gain that was not reversed once the study ended [147].

A randomized, double blind, placebo controlled trial studied patients with diabetes or pre-diabetes and biopsy proven NASH. Every patient was recommended a low calorie diet and assigned to pioglitazone or a placebo for 18 months. 58% of patients taking pioglitazone had reduction in at least 2 points on the NAFLD activity score ($p<0.05$) and 51% had resolution of NASH ($p<0.05$). The pioglitazone group, similar to the PIVENS trial, also had greater weight gain (2.5 kg) than the placebo group. Overall, pioglitazone was found to be safe and effective for diabetic and pre-diabetic patients with NASH [148]. Pioglitazone has also been studied in PD and found to be an efficacious treatment for plaque psoriasis, leading to a significant decrease in mean PASI scores and increase in PASI-75 scores (Table 2) [149,150].

Given these limitations in current treatments for NAFLD, multiple studies are underway to assess the efficacy of new therapeutics. Promising medications in phase II and III of clinical trials for NAFLD/NASH include farnesoid X receptor (FXR) agonists, glucagon like peptide (GLP-1) agonists, fatty acid synthase/stearoyl-CoA desaturase (FASN/SCD1) inhibitors, and thyroid hormone receptor beta (THR-beta) agonists. These drugs fall into four main categories – metabolic targets such as those that improve insulin sensitivity or reduce lipogenesis, inflammatory pathway targets, bile acid modulation targets, and anti-fibrotic targets in the liver. Moreover, emerging therapeutics are also highlighting extra-hepatic benefits such as improving insulin resistance, hyperlipidemia and weight loss which may also impact diseases like PD [151].

Obeticholic acid, an FXR agonist, works via bile acid modulation and regulates lipid homeostasis and promotes insulin sensitivity. Compared to placebo, obeticholic acid demonstrated significant improvement in liver fibrosis in NASH patients in the REGENERATE trial (23% versus 12%; $p = 0.0002$). GLP-1 agonists, such as liraglutide and semaglutide, are approved for the treatment of Type II Diabetes Mellitus and are currently being studied for NAFLD. Initial studies showed resolution of NASH in 39% of patients in the liraglutide group compared with 9% of patients in the placebo group ($p<0.001$). However, there was no statistically significant difference when adjusting for weight loss, suggesting the reduction in steatohepatitis may be all modulated by weight loss and not by the GLP-1 agonist itself (Table 2) [151].

A larger, Phase 2 clinical trial evaluating semaglutide demonstrated benefit compared to placebo for resolution of NASH. It also demonstrated a dose response relationship with those receiving higher doses of the semaglutide exhibiting higher rates of NASH resolution (59% vs 17%; $p<0.001$) [151]. Both FXR agonists and GLP-1 agonists may be beneficial in PD since they target pathways of insulin sensitivity and TNF-alpha/IL-6 mediated inflammation. A recent RCT of liraglutide administration in patients PsO and T2DM demonstrated a significant decrease in PASI scores after 12 weeks. In addition, these patients also showed decreased expression of IL-17, IL-23 and TNF-alpha on the skin biopsy (Table 2) [152].

SCD-1 inhibitors such as aramchol, a conjugate of a bile acid and fatty acid, are also being studied for their effects on reducing liver steatosis. A three month proof of concept trial found that aramchol has a dose-dependent effect on hepatic steatosis. A phase IIb clinical trial, however, showed no significant difference in NASH resolution compared to placebo (16.7% vs 5%; $p = 0.051$) so an additional larger study is underway to further evaluate the drug's potential (Table 2) [151].

THR-beta is the major form of thyroid hormone receptor expressed in the liver. THR-beta is involved in hepatic triglyceride and cholesterol metabolism so THR-beta agonists like resmetirom should not only improve NAFLD but also have additional metabolic benefits. Phase IIb clinical trial showed relative reduction in liver fat compared to placebo (−36.3% vs −9.6%; $p < 0.0001$) and higher rates of NASH resolution compared to placebo (27.4% vs 6.5%; $p= 0.02$). In addition, resmetirom reduced LDL cholesterol by 22.3% and triglycerides by 30.8% compared to placebo ($p< 0.0001$ for all lipids). In this way, THR-beta agonists may be potentially efficacious for PD by reducing triglycerides and inflammatory lipid pathways (Table 2) [151].

Conclusion

It is clear that there is an increased prevalence of NAFLD in psoriatic disease patients which likely stems from a common pathway of disease and less likely as a consequence of treatment for PD. An understanding of the underlying pathophysiology of NAFLD in patients with PD can help guide treatment. Moreover, identifying targets in these common disease pathways could help guide research into drug targets of therapeutics that can treat both disease states simultaneously. Further studies investigating the impact of biologics on NAFLD and NAFLD therapeutics on PD are needed. We hypothesize that intervening in the pathogenesis of metabolic stress and inflammation as described in this review would be potentially successful to target both diseases. Current clinical trials for therapeutics such as GLP-1 agonists and THR-beta agonists seek to target these shared pathways of insulin resistance, lipid homeostasis and systemic inflammation, and may ultimately be beneficial therapies for patients with coexisting PD and NAFLD.

Funding

RL receives funding support from NIEHS (5P42ES010337), NCATS (5UL1TR001442), NIDDK (U01DK061734, R01DK106419, P30DK120515, R01DK121378, R01DK124318), NHLBI (P01HL147835), and DOD PRCRP (W81XWH-18-2-0026). VA is supported by NIDDK (K23DK119460). MG receives funding support from NIAMS

(R01AR073324). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

[1]. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet 2018;391:2273–84. [PubMed: 29893226]

[2]. Mease PJ, 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. [PubMed: 23981683]

[3]. Armstrong AW, et al. Psoriasis prevalence in adults in the United States. JAMA Dermatol 2021;157:940–6. [PubMed: 34190957]

[4]. Takeshita J, et al. Psoriasis and comorbid diseases: epidemiology. J Am Acad Dermatol 2017;76:377–90. [PubMed: 28212759]

[5]. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell 2021;184:2537–64. [PubMed: 33989548]

[6]. Adams LA, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113–21. [PubMed: 16012941]

[7]. Loomba R, Adams LA. The 20% Rule of NASH progression: the natural history of advanced fibrosis and cirrhosis caused by NASH. Hepatology 2019;70:1885–8. [PubMed: 31520407]

[8]. Bellinato F, Gisondi P, Mantovani A, Girolomoni G, Targher G. Risk of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis: an updated systematic review and meta-analysis of observational studies. J Endocrinol Invest 2022;45:1277–88. [PubMed: 35147926]

[9]. Yeung H, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. JAMA Dermatol 2013;149:1173–9. [PubMed: 23925466]

[10]. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009;51:758–64. [PubMed: 19560226]

[11]. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. Int J Mol Sci 2019;20:1475. [PubMed: 30909615]

[12]. Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. N Engl J Med 2017;377:2063–72. [PubMed: 29166236]

[13]. Jiménez-Cortegana C, et al. Role of leptin in non-alcoholic fatty liver disease. Biomedicines 2021;9:762. [PubMed: 34209386]

[14]. Mantovani A, Gisondi P, Lonardo A, Targher G. Relationship between non-alcoholic fatty liver disease and psoriasis: a novel hepato-dermal axis? Int J Mol Sci 2016;17:217. [PubMed: 26861300]

[15]. Prussick R, Prussick L, Nussbaum D. Nonalcoholic fatty liver disease and psoriasis. J Clin Aesthet Dermatol 2015;8:43–5.

[16]. van der Voort EAM, et al. Psoriasis is independently associated with nonalcoholic fatty liver disease in patients 55 years old or older: results from a population-based study. J Am Acad Dermatol 2014;70:517–24. [PubMed: 24373781]

[17]. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr 2008;88:1242–7. [PubMed: 18996858]

[18]. Polic MV, et al. Psoriasis severity—a risk factor of insulin resistance independent of metabolic syndrome. Int J Environ Res Public Health 2018;15:1486. [PubMed: 30011841]

[19]. Karadag AS, et al. Is psoriasis a pre-atherosderotic disease? Increased insulin resistance and impaired endothelial function in patients with psoriasis. Int J Dermatol 2010;49:642–6. [PubMed: 20618468]

[20]. Boehncke S, et al. Psoriasis patients show signs of insulin resistance. Br J Dermatol 2007;157:1249–51. [PubMed: 17916217]

[21]. Divella R, Mazzocca A, Daniele A, Sabbà C, Paradiso A. Obesity, nonalcoholic fatty liver disease and adipocytokines network in promotion of cancer. Int J Biol Sci 2019;15:610–6. [PubMed: 30745847]

[22]. 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. [PubMed: 23208415]

[23]. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology 1990;12:1106–10. [PubMed: 2227807]

[24]. Jensen P, Skov L. Psoriasis and obesity. Dermatology 2016;232:633–9. [PubMed: 28226326]

[25]. Lihn AS, Pedersen SB, Richelsen B. Adiponectin: action, regulation and association to insulin sensitivity. Obes Rev 2005;6:13–21. [PubMed: 15655035]

[26]. Matsuzawa Y Establishment of a concept of visceral fat syndrome and discovery of adiponectin. Proc Jpn Acad Ser B 2010;86:131–41. [PubMed: 20154470]

[27]. Xu A, et al. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. J Clin Invest 2003;112:91–100. [PubMed: 12840063]

[28]. Folco EJ, Rocha VZ, López-Ilasaca M, Libby P. Adiponectin inhibits pro-inflammatory signaling in human macrophages independent of interleukin-10. J Biol Chem 2009;284:25569–75. [PubMed: 19617629]

[29]. Shibata S, et al. Adiponectin regulates psoriasiform skin inflammation by suppressing IL-17 production from γδ-T cells. Nat Commun 2015;6:7687. [PubMed: 26173479]

[30]. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochem Biophys Res Commun 2004;323:630–5. [PubMed: 15369797]

[31]. Kyriakou A, Patsatsi A, Sotiriadis D, Goulis DG. Serum leptin, resistin, and adiponectin concentrations in psoriasis: a meta-analysis of observational studies. Dermatology 2017;233:378–89. [PubMed: 29232663]

[32]. Coimbra S, et al. Circulating levels of adiponectin, oxidized LDL and C-reactive protein in Portuguese patients with psoriasis vulgaris, according to body mass index, severity and duration of the disease. J Dermatol Sci 2009;55:202–4. [PubMed: 19576730]

[33]. Yamauchi T, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8:1288–95. [PubMed: 12368907]

[34]. Targher G, et al. Associations between plasma adiponectin concentrations and liver histology in patients with nonalcoholic fatty liver disease. Clin Endocrinol 2006;64:679–83.

[35]. Zelber-Sagi S, et al. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. J Hepatol 2012;56:1145–51. [PubMed: 22245895]

[36]. Santos-Alvarez J, Goberna R, Sánchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. Cell Immunol 1999;194:6–11. [PubMed: 10357875]

[37]. Houseknecht KL, Baile CA, Matteri RL, Spurlock ME. The biology of leptin: a review. J Anim Sci 1998;76:1405–20. [PubMed: 9621947]

[38]. Hamminga EA, van der Lely AJ, Neumann HaM, Thio HB. Chronic inflammation in psoriasis and obesity: implications for therapy. Med Hypotheses 2006;67:768–73. [PubMed: 16781085]

[39]. Xue K, et al. Leptin induces secretion of pro-inflammatory cytokines by human keratinocytes in vitro–a possible reason for increased severity of psoriasis in patients with a high body mass index. Exp Dermatol 2013;22:406–10. [PubMed: 23711065]

[40]. Wang Y, et al. Psoriasis is associated with increased levels of serum leptin. Br J Dermatol 2008;158:1134–5. [PubMed: 18294316]

[41]. Cerman AA, et al. Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. Br J Dermatol 2008;159:820–6. [PubMed: 18637894]

[42]. German JP, et al. Leptin deficiency causes insulin resistance induced by uncontrolled diabetes. Diabetes 2010;59:1626–34. [PubMed: 20424233]

[43]. Ikejima K, et al. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. Hepatology 2001;34:288–97. [PubMed: 11481614]

[44]. Marra F. Leptin and liver fibrosis: a matter of fat. Gastroenterology 2002;122:1529–32. [PubMed: 11984539]

[45]. Rotundo L, Persaud A, Feurdean M, Ahlawat S, Kim H. The Association of leptin with severity of non-alcoholic fatty liver disease: a population-based study. Clin Mol Hepatol 2018;24:392–401. [PubMed: 30068065]

[46]. Liu Y, Krueger JG, Bowcock AM. Psoriasis: genetic associations and immune system changes. Genes Immun 2007;8:1–12. [PubMed: 17093502]

[47]. Vonghia L, Michielsen P, Francque S. Immunological mechanisms in the pathophysiology of non-alcoholic steatohepatitis. Int J Mol Sci 2013;14:19867–90. [PubMed: 24084730]

[48]. Tobin A-M, Kirby B TNF alpha inhibitors in the treatment of psoriasis and psoriatic arthritis. BioDrugs 2005;19:47–57. [PubMed: 15691217]

[49]. Al-Mutairi N, Shabaan D. Effects of tumor necrosis factor α inhibitors extend beyond psoriasis: insulin sensitivity in psoriasis patients with type 2 diabetes mellitus. Cutis 2016;97:235–41. [PubMed: 27023086]

[50]. Nieto-Vazquez I, et al. Insulin resistance associated to obesity: the link TNF-alpha. Arch Physiol Biochem 2008;114:183–94. [PubMed: 18629684]

[51]. Shuh M, Bohorquez H, Loss GE, Cohen AJ. Tumor necrosis factor-α: life and death of hepatocytes during liver ischemia/reperfusion injury. Ochsner J 2013;13:119–30. [PubMed: 23531747]

[52]. Feldstein AE, et al. Free fatty acids promote hepatic lipotoxicity by stimulating TNF-alpha expression via a lysosomal pathway. Hepatology 2004;40:185–94. [PubMed: 15239102]

[53]. Carter-Kent C, Zein NN, Feldstein AE. Cytokines in the pathogenesis of fatty liver and disease progression to steatohepatitis: implications for treatment. Am J Gastroenterol 2008;103:1036–42. [PubMed: 18177455]

[54]. Crespo J, et al. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. Hepatology 2001;34:1158–63. [PubMed: 11732005]

[55]. Harper EG, et al. Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. J Invest Dermatol 2009;129:2175–83. [PubMed: 19295614]

[56]. Lowes MA, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol 2008;128:1207–11. [PubMed: 18200064]

[57]. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. J Immunol 2018;201:1605–13. [PubMed: 30181299]

[58]. Wang CQF, et al. IL-17 and TNF synergistically modulate cytokine expression while suppressing melanogenesis: potential relevance to psoriasis. J Invest Dermatol 2013;133:2741–52. [PubMed: 23732752]

[59]. van Baarsen LG, 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. [PubMed: 25146432]

[60]. Mitra A, Raychaudhuri SK, Raychaudhuri SP. Functional role of IL-22 in psoriatic arthritis. Arthritis Res Ther 2012;14:R65. [PubMed: 22417743]

[61]. Boutet M-A, Nerviani A, Gallo Afflitto G, Pitzalis C. Role of the IL-23/IL-17 axis in psoriasis and psoriatic arthritis: the clinical importance of its divergence in skin and joints. Int J Mol Sci 2018;19:E530.

[62]. Sakkas LI, Bogdanos DP. Are psoriasis and psoriatic arthritis the same disease? The IL-23/IL-17 axis data. Autoimmun Rev 2017;16:10–5. [PubMed: 27666819]

[63]. Adamopoulos IE, et al. IL-17A gene transfer induces bone loss and epidermal hyperplasia associated with psoriatic arthritis. Ann Rheum Dis 2015;74:1284–92. [PubMed: 24567524]

[64]. Gomes AL, et al. Metabolic inflammation-associated IL-17A causes non-alcoholic steatohepatitis and hepatocellular carcinoma. Cancer Cell 2016;30:161–75. [PubMed: 27411590]

[65]. Shen T, et al. Interleukin-17A exacerbates high-fat diet-induced hepatic steatosis by inhibiting fatty acid β-oxidation. Biochim Biophys Acta Mol Basis Dis 2017;1863:1510–8. [PubMed: 28153707]

[66]. Tang K-Y, et al. Safety, pharmacokinetics, and biomarkers of F-652, a recombinant human interleukin-22 dimer, in healthy subjects. Cell Mol Immunol 2019;16:473–82. [PubMed: 29670279]

[67]. Malhi H, Bronk SF, Werneburg NW, Gores GJ. Free fatty acids induce JNK-dependent hepatocyte lipoapoptosis. J Biol Chem 2006;281:12093–101. [PubMed: 16505490]

[68]. Rolla S, et al. The balance between IL-17 and IL-22 produced by liver-infiltrating T-helper cells critically controls NASH development in mice. Clin Sci (Lond) 2016;130:193–203. [PubMed: 26558403]

[69]. Kodama Y, et al. c-Jun N-terminal kinase-1 from hematopoietic cells mediates progression from hepatic steatosis to steatohepatitis and fibrosis in mice. Gastroenterology 2009;137. 1467–77.e5. [PubMed: 19549522]

[70]. Fabre T, Kared H, Friedman SL, Shoukry NH. IL-17A enhances the expression of profibrotic genes through upregulation of the TGF-β receptor on hepatic stellate cells in a JNK-dependent manner. J Immunol 2014;193:3925–33. [PubMed: 25210118]

[71]. Wolk K, et al. IL-22 increases the innate immunity of tissues. Immunity 2004;21:241–54. [PubMed: 15308104]

[72]. Nograles KE, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol 2008;159:1092–102. [PubMed: 18684158]

[73]. Boniface K, et al. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol 2005;174:3695–702. [PubMed: 15749908]

[74]. Benham H, et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. Arthritis Res Ther 2013;15:R136. [PubMed: 24286492]

[75]. Haley EK, et al. The impact of genetic background and sex on the phenotype of IL-23 induced murine spondyloarthritis. PLoS ONE 2021;16:e0247149. [PubMed: 33983951]

[76]. Reinhardt A, et al. Interleukin-23–Dependent γ/δ T cells produce interleukin-17 and accumulate in the enthesis, aortic valve, and ciliary body in mice. Arthritis & Rheumatology 2016;68:2476–86. [PubMed: 27111864]

[77]. Bouchareychas L, Grössinger EM, Kang M, Adamopoulos IE. γδTCR regulates production of interleukin-27 by neutrophils and attenuates inflammatory arthritis. Sci Rep 2018;8:7590. [PubMed: 29765156]

[78]. Liang SC, et al. IL-22 induces an acute-phase response. J Immunol 2010;185:5531–8. [PubMed: 20870942]

[79]. Radaeva S, Sun R, Pan H-N, Hong F, Gao B. Interleukin 22 (IL-22) plays a protective role in T cell-mediated murine hepatitis: IL-22 is a survival factor for hepatocytes via STAT3 activation. Hepatology 2004;39:1332–42. [PubMed: 15122762]

[80]. Park O, et al. In vivo consequences of liver-specific interleukin-22 expression in mice: implications for human liver disease progression. Hepatology 2011;54:252–61. [PubMed: 21465510]

[81]. Grossman RM, et al. Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. Proc Natl Acad Sci 1989;86:6367–71. [PubMed: 2474833]

[82]. Neuner P, et al. Increased IL-6 production by monocytes and keratinocytes in patients with psoriasis. J Invest Dermatol 1991;97:27–33. [PubMed: 2056189]

[83]. Mizutani H, Ohmoto Y, Mizutani T, Murata M, Shimizu M. Role of increased production of monocytes TNF-alpha, IL-lbeta and IL-6 in psoriasis: relation to focal infection, disease activity and responses to treatments. J Dermatol Sci 1997;14:145–53. [PubMed: 9039978]

[84]. Bettelli E, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006;441:235–8. [PubMed: 16648838]

[85]. Comparative genomic profiling of synovium versus skin lesions in psoriatic arthritis - Belasco -. Wiley Online Library; 2015. - Arthritis & Rheumatology -, https://onlinelibrary.wiley.com/doi/10.1002/art.38995.

[86]. Altobelli E, Angeletti PM, Piccolo D, De Angelis R. Synovial fluid and serum concentrations of inflammatory markers in rheumatoid arthritis, psoriatic arthritis and osteoarthitis: a systematic review. Curr Rheumatol Rev 2017;13:170–9. [PubMed: 28460627]

[87]. Spadaro A, et al. Interleukin-6 and soluble interleukin-2-receptor in psoriatic arthritis: correlations with clinical and laboratory parameters. Clin Exp Rheumatol 1996;14:413–6. [PubMed: 8871841]

[88]. Ogata A, Kumanogoh A, Tanaka T. Pathological role of interleukin-6 in psoriatic arthritis. Arthritis 2012;2012:713618. [PubMed: 23133751]

[89]. Wieckowska A, et al. Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. Am J Gastroenterol 2008;103:1372–9. [PubMed: 18510618]

[90]. Lee E, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med 2004;199:125–30. [PubMed: 14707118]

[91]. Kim J, Krueger JG. Highly effective new treatments for psoriasis target the IL-23/Type 17 T cell autoimmune axis. Annu Rev Med 2017;68:255–69. [PubMed: 27686018]

[92]. Chan TC, Hawkes JE, Krueger JG. Interleukin 23 in the skin: role in psoriasis pathogenesis and selective interleukin 23 blockade as treatment. Ther Adv Chronic Dis 2018;9:111–9. [PubMed: 29796240]

[93]. Lubberts E The IL-23-IL-17 axis in inflammatory arthritis. Nat Rev Rheumatol 2015;11:415–29. [PubMed: 25907700]

[94]. Polyfunctional, Proinflammatory. Tissue-Resident memory phenotype and function of synovial interleukin-17A+CD8+ T cells in psoriatic arthritis - Steel -. Wiley Online Library; 2020. - Arthritis & Rheumatology -, https://onlinelibrary.wiley.com/doi/10.1002/art.41156.

[95]. Tang Y, et al. Interleukin-17 exacerbates hepatic steatosis and inflammation in non-alcoholic fatty liver disease. Clin Exp Immunol 2011;166:281–90. [PubMed: 21985374]

[96]. Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol 2017;67:829–46. [PubMed: 28545937]

[97]. Wong VW-S, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol 2018;69:1349–56. [PubMed: 30142427]

[98]. Petersen KF, et al. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes 2005;54:603–8. [PubMed: 15734833]

[99]. Promrat K, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121–9. [PubMed: 19827166]

[100]. Vilar-Gomez E, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367–78. .e5; quiz e14-15. [PubMed: 25865049]

[101]. Jensen P, et al. Effect of weight loss on the severity of psoriasis: a randomized clinical study. JAMA Dermatol 2013;149:795–801. [PubMed: 23752669]

[102]. Naldi L, et al. Diet and physical exercise in psoriasis: a randomized controlled trial. Br J Dermatol 2014;170:634–42. [PubMed: 24641585]

[103]. Al-Mutairi N, Nour T. The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. Expert Opin Biol Ther 2014;14:749–56. [PubMed: 24661040]

[104]. Ryan MC, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol 2013;59:138–43. [PubMed: 23485520]

[105]. Kontogianni MD, et al. Adherence to the Mediterranean diet is associated with the severity of non-alcoholic fatty liver disease. Clin Nutr 2014;33:678–83. [PubMed: 24064253]

[106]. Phan C, et al. Association between mediterranean anti-inflammatory dietary profile and severity of psoriasis: results from the NutriNet-Sante cohort. JAMA Dermatol 2018;154:1017–24. [PubMed: 30046840]

[107]. Araújo EP, et al. Infliximab restores glucose homeostasis in an animal model of diet-induced obesity and diabetes. Endocrinology 2007;148:5991–7. [PubMed: 17761768]

[108]. Barbuio R, Milanski M, Bertolo MB, Saad MJ, Velloso LA. Infliximab reverses steatosis and improves insulin signal transduction in liver of rats fed a high-fat diet. J Endocrinol 2007;194:539–50. [PubMed: 17761893]

[109]. Koca SS, et al. The treatment with antibody of TNF-alpha reduces the inflammation, necrosis and fibrosis in the non-alcoholic steatohepatitis induced by methionine and choline deficient diet. Inflammation 2008;31:91–8. [PubMed: 18066656]

[110]. Yalcin M, et al. A comparison of the effects of infliximab, adalimumab, and pentoxifylline on rats with non-alcoholic steatohepatitis. Turk J Gastroenterol 2014;25(Suppl 1):167–75. [PubMed: 25910299]

[111]. Seitz M, et al. Hepatoprotective effect of tumour necrosis factor alpha blockade in psoriatic arthritis: a cross-sectional study. Ann Rheum Dis 2010;69:1148–50. [PubMed: 19854710]

[112]. Campanati 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. [PubMed: 23065020]

[113]. Smolen JS, et al. Multicentre, randomised, open-label, parallel-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naive to biological disease-modifying antirheumatic drug: final results by week 52. Ann Rheum Dis 2020;79:1310–9. [PubMed: 32660977]

[114]. Gerdes S, Pinter A, Papavassilis C, Reinhardt M. Effects of secukinumab on metabolic and liver parameters in plaque psoriasis patients. J Eur Acad Dermatol Venereol 2020;34:533–41. [PubMed: 31599476]

[115]. Zai W, et al. Targeted interleukin-22 gene delivery in the liver by polymetformin and penetratin-based hybrid nanoparticles to treat nonalcoholic fatty liver disease. ACS Appl Mater Interfaces 2019;11:4842–57. [PubMed: 30628769]

[116]. Yang L, et al. Amelioration of high fat diet induced liver lipogenesis and hepatic steatosis by interleukin-22. J Hepatol 2010;53:339–47. [PubMed: 20452699]

[117]. Arab JP, et al. An open-label, dose-escalation study to assess the safety and efficacy of IL-22 agonist F-652 in patients with alcohol-associated hepatitis. Hepatology 2020;72:441–53. [PubMed: 31774566]

[118]. Rothenberg ME, et al. Randomized Phase I Healthy Volunteer Study of UTTR1147A (IL-22Fc): a potential therapy for epithelial injury. Clin Pharmacol Ther 2019;105:177–89. [PubMed: 29952004]

[119]. Pfizer. A single dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics and clinical activity Of ILV-095 administered subcutaneously to subjects with psoriasis. 2017. https://dinicaltrials.gov/ct2/show/NCT01010542.

[120]. Galle-Treger L, et al. Autophagy impairment in liver CD11c+ cells promotes non-alcoholic fatty liver disease through production of IL-23. Nat Commun 2022;13:1440. [PubMed: 35301333]

[121]. Gelfand JM, et al. A Phase IV, randomized, double-blind, placebo-controlled crossover study of the effects of ustekinumab on vascular inflammation in psoriasis (the VIP-U Trial). J Invest Dermatol 2020;140. 85–93.e2.

[122]. Llamas-Velasco M, Concha-Garzón MJ, García-Diez A, Daudén E. Liver injury in psoriasis patients receiving ustekinumab: a retrospective study of 44 patients treated in the clinical practice setting. Actas Dermosifiliogr 2015;106:470–6. [PubMed: 25912374]

[123]. Mease PJ, et al. The efficacy and safety of clazakizumab, an anti-interleukin-6 monodonal antibody, in a phase IIb study of adults with active psoriatic arthritis. Arthritis Rheumatol 2016;68:2163–73. [PubMed: 27059799]

[124]. Wendling D, Letho-Gyselinck H, Guillot X, Prati C. Psoriasis onset with tocilizumab treatment for rheumatoid arthritis. J Rheumatol 2012;39:657. [PubMed: 22383356]

[125]. Laurent S, Le Parc J-M, Clérici T, Bréban M, Mahé E. Onset of psoriasis following treatment with tocilizumab. Br J Dermatol 2010;163:1364–5. [PubMed: 20731650]

[126]. Matsushima Y, et al. Psoriasiform dermatitis developing during treatment of juvenile idiopathic arthritis with tocilizumab. Case Rep Dermatol 2019;11:317–21. [PubMed: 31911769]

[127]. Wahlang B, McClain C, Barve S, Gobejishvili L. Role of cAMP and phosphodiesterase signaling in liver health and disease. Cell Signal 2018;49:105–15. [PubMed: 29902522]

[128]. Xu Z, et al. Coenzyme Q10 improves lipid metabolism and ameliorates obesity by regulating CaMKII-mediated PDE4 inhibition. Sci Rep 2017;7:8253. [PubMed: 28811612]

[129]. Zhang R, Maratos-Flier E, Flier JS. Reduced Adiposity and high-fat diet-induced adipose inflammation in mice deficient for phosphodiesterase 4B. Endocrinology 2009;150:3076–82. [PubMed: 19359377]

[130]. Ong WK, et al. The role of the PDE4D cAMP phosphodiesterase in the regulation of glucagon-like peptide-1 release. Br J Pharmacol 2009;157:633–44. [PubMed: 19371330]

[131]. Ratziu V, et al. Lack of efficacy of an inhibitor of PDE4 in phase 1 and 2 trials of patients with nonalcoholic steatohepatitis. Clinic Gastroenterol Hepatol 2014;12. 1724–30. e5.

[132]. Cutolo M, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 Trial. J Rheumatol 2016;43:1724–34. [PubMed: 27422893]

[133]. Mazzilli S, et al. Real life experience of apremilast in psoriasis and arthritis psoriatic patients: preliminary results on metabolic biomarkers. J Dermatol 2020;47:578–82. [PubMed: 32239555]

[134]. Lubrano E, Scriffignano S, Perrotta FM. Abatacept for the treatment of psoriatic arthritis. Expert Rev Clin Immunol 2018;14:899–905. [PubMed: 30246575]

[135]. Sombetzki M, et al. Preventive CTLA-4-Ig treatment reduces hepatic EGG load and hepatic fibrosis in schistosoma mansoni-infected mice. Biomed Res Int 2019;2019:1704238. [PubMed: 31950032]

[136]. Boleto G, et al. T-cell costimulation blockade is effective in experimental digestive and lung tissue fibrosis. Arthritis Res Ther 2018;20:197. [PubMed: 30157927]

[137]. Peeters AJ, Dukmans BAC, Van Der Schroeff JG. Fumaric acid therapy for psoriatic arthritis. A randomized, double-blind, placebo-controlled study. Rheumatology 1992;31:502–4.

[138]. Mrowietz U, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm® - and placebo-controlled trial (BRIDGE). Br J Dermatol 2017;176:615–23. [PubMed: 27515097]

[139]. Vandermeeren M, Janssens S, Borgers M, Geysen J. Dimethylfumarate is an inhibitor of cytokine-induced E-selectin, VCAM-1, and ICAM-1 expression in human endothelial cells. Biochem Biophys Res Commun 1997;234:19–23. [PubMed: 9168952]

[140]. Sebök B, Bonnekoh B, Mahrle G. IL-1 alpha-induced expression of ICAM-1 on cultured hyperproliferative keratinocytes: suppression by antipsoriatic dimethylfumarate. Int J Dermatol 1994;33:367–70. [PubMed: 7913702]

[141]. Thio HB, et al. Fumaric acid derivatives evoke a transient increase in intracellular free calcium concentration and inhibit the proliferation of human keratinocytes. Br J Dermatol 1994;131:856–61. [PubMed: 7857839]

[142]. Sangineto M, et al. Dimethyl fumarate ameliorates hepatic inflammation in alcohol related liver disease. Liver Int 2020;40:1610–9. [PubMed: 32306456]

[143]. Zhang Y, et al. Computational repositioning of dimethyl fumarate for treating alcoholic liver disease. Cell Death Dis 2020;11:1–14. [PubMed: 31911576]

[144]. Dwivedi DK, Jena G, Kumar V. Dimethyl fumarate protects thioacetamide-induced liver damage in rats: studies on Nrf2, NLRP3, and NF-κB. J Biochem Mol Toxicol 2020;34:e22476. [PubMed: 32060995]

[145]. Abdelrahman RS, Abdel-Rahman N. Dimethyl fumarate ameliorates acetaminophen-induced hepatic injury in mice dependent of Nrf-2/HO-1 pathway. Life Sci 2019;217:251–60. [PubMed: 30550888]

[146]. Balak DM, Piaserico S, Kasujee I. Non-Alcoholic Fatty Liver Disease (NAFLD) in patients with psoriasis: a review of the hepatic effects of systemic therapies. PTT 2021;11:151–68.

[147]. Sanyal AJ, et al. Pioglitazone, Vitamin E, or Placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675–85. [PubMed: 20427778]

[148]. Cusi K, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016;165:305–15. [PubMed: 27322798]

[149]. Chi C-C, et al. Effects of antidiabetic drugs on psoriasis: a meta-analysis. Eur J Clin Invest 2021;51:e13377. [PubMed: 32914429]

[150]. Chang G, Wang J, Song J, Zhang Z, Zhang L. Efficacy and safety of pioglitazone for treatment of plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials. J Dermatolog Treat 2020;31:680–6. [PubMed: 31116619]

[151]. Vuppalanchi R, Noureddin M, Alkhouri N, Sanyal AJ. Therapeutic pipeline in nonalcoholic steatohepatitis. Nat Rev Gastroenterol Hepatol 2021;18:373–92. [PubMed: 33568794]

[152]. Lin L, et al. Glucagon-like peptide-1 receptor agonist liraglutide therapy for psoriasis patients with type 2 diabetes: a randomized-controlled trial. J Dermatolog Treat 2020:1–7. 10.1080/09546634.2020.1826392.

[153]. McInnes IB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013;382:780–9. [PubMed: 23769296]

[154]. Ritchlin C, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 2014;73:990–9. [PubMed: 24482301]

[155]. Griffiths CEM, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118–28. [PubMed: 20071701]

[156]. Kimball AB, et al. Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. Ann Intern Med 2012;157:846–55. [PubMed: 23247938]

[157]. Tsai T-F, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci 2011;63:154–63. [PubMed: 21741220]

[158]. Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675–84. [PubMed: 18486740]

[159]. Mease PJ, et al. Efficacy and safety of tildrakizumab in patients with active psoriatic arthritis: results of a randomised, double-blind, placebo-controlled, multiple-dose, 52-week phase lib study. Ann Rheum Dis 2021;80:1147–57. [PubMed: 33985942]

[160]. Papp K, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol 2015;73:37–49. [PubMed: 26089047]

[161]. Reich K, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol 2017;76:418–31. [PubMed: 28057361]

[162]. Blauvelt A, et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. Br J Dermatol 2018;179:615–22. [PubMed: 29742274]

[163]. Reich K, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. Br J Dermatol 2020;182:605–17. [PubMed: 31218661]

[164]. Mease PJ, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1126–36. [PubMed: 32178766]

[165]. Deodhar A, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2018;391:2213–24. [PubMed: 29893222]

[166]. Langley RG, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. Br J Dermatol 2018;178:114–23. [PubMed: 28635018]

[167]. Blauvelt A, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol 2017;76:405–17. [PubMed: 28057360]

[168]. Gordon KB, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. N Engl J Med 2015;373:136–44. [PubMed: 26154787]

[169]. Östór A, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. Ann Rheum Dis 2022;81:351–8. [PubMed: 34815219]

[170]. Kristensen LE, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. Ann Rheum Dis 2022;81:225–31. [PubMed: 34911706]

[171]. Papp KA, et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. N Engl J Med 2017;376:1551–60. [PubMed: 28423301]

[172]. Papp KA, et al. Long-term efficacy and safety of risankizumab for the treatment of moderate-to-severe plaque psoriasis: interim analysis of the LIMMitless open-label extension trial beyond 3 years of follow-up. Br J Dermatol 2021;185:1135–45. [PubMed: 34157132]

[173]. Blauvelt A, et al. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy, safety and speed of response from a randomized, double-blinded trial. Br J Dermatol 2020;182:1348–58. [PubMed: 31887225]

[174]. Mease PJ, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76:79–87. [PubMed: 27553214]

[175]. Nash P, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017;389:2317–27. [PubMed: 28551073]

[176]. Mease PJ, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis 2020;79:123–31. [PubMed: 31563894]

[177]. Griffiths CEM, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet 2015;386:541–51. [PubMed: 26072109]

[178]. Xu R, Tao A, Zhang S, Zhang M. Neutralization of interleukin-17 attenuates high fat diet-induced non-alcoholic fatty liver disease in mice. Acta Biochim Biophys Sin (Shanghai) 2013;45:726–33. [PubMed: 23786840]

[179]. McInnes IB, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137–46. [PubMed: 26135703]

[180]. Mease PJ, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373:1329–39. [PubMed: 26422723]

[181]. Langley RG, et al. Secukinumab in plaque psoriasis — results of two phase 3 trials. N Engl J Med 2014;371:326–38. [PubMed: 25007392]

[182]. Thaçi D, et al. Secukimimab is superior to ustekinumab in dearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol 2015;73:400–9. [PubMed: 26092291]

[183]. Blauvelt A, et al. Secukinumab is superior to ustekinumab in dearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. J Am Acad Dermatol 2017;76:60–9. e9. [PubMed: 27663079]

[184]. Mease PJ, et al. Brodalumab, an anti-IL17RA monodonal antibody, in psoriatic arthritis. N Engl J Med 2014;370:2295–306. [PubMed: 24918373]

[185]. Mease PJ, Helliwell PS, Hjuler KF, Raymond K, McInnes I. Brodalumab in psoriatic arthritis: results from the randomised phase III AMVISION-1 and AMVISION-2 trials. Ann Rheum Dis 2021;80:185–93. [PubMed: 33106286]

[186]. Papp KA, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol 2016;175:273–86. [PubMed: 26914406]

[187]. Lebwohl M, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med 2015;373:1318–28. [PubMed: 26422722]

[188]. Nakagawa H, Niiro H, Ootaki K. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: efficacy and safety results from a phase II randomized controlled study. J Dermatol Sci 2016;81:44–52. [PubMed: 26547109]

[189]. Zheng Q, et al. Lack of FGF21 promotes NASH-HCC transition via hepatocyte-TLR4-IL-17A signaling. Theranostics 2020;10:9923–36. [PubMed: 32929325]

[190]. Antoni CE, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum 2005;52:1227–36. [PubMed: 15818699]

[191]. Antoni C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150–7. [PubMed: 15677701]

[192]. Kavanaugh A, et al. Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis. Ann Rheum Dis 2006;65:471–7. [PubMed: 16096330]

[193]. Menter A, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007;56:31. e1–15.

[194]. Reich K, et al. Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: results of a randomized, long-term extension trial (RESTORE2). Br J Dermatol 2013;168:1325–34. [PubMed: 23621698]

[195]. Barker J, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol 2011;165:1109–17. [PubMed: 21910713]

[196]. Chaudhari U, et al. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet 2001;357:1842–7. [PubMed: 11410193]

[197]. Mease PJ, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52:3279–89. [PubMed: 16200601]

[198]. Genovese MC, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol 2007;34:1040–50. [PubMed: 17444593]

[199]. Gladman DD, et al. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. Ann Rheum Dis 2007;66:163–8. [PubMed: 17046964]

[200]. Saurat J-H, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158:558–66. [PubMed: 18047523]

[201]. Menter A, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol 2008;58:106–15. [PubMed: 17936411]

[202]. Gordon K, et al. Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL. J Am Acad Dermatol 2012;66:241–51. [PubMed: 21752491]

[203]. Mease PJ, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis 2014;73:48–55. [PubMed: 23942868]

[204]. Gladman D, Fleischmann R, Coteur G, Woltering F, Mease PJ. Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. Arthritis Care Res 2014;66:1085–92.

[205]. Reich K, et al. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: results of a phase II randomized, placebo-controlled trial with a re-treatment extension. Br J Dermatol 2012;167:180–90. [PubMed: 22413944]

[206]. Dattola A, Cannizzaro MV, Mazzeo M, Bianchi L. Certolizumab pegol in the treatment of psoriasis and psoriatic arthritis: preliminary real-life data. Dermatol Ther 2017;7:485–92.

[207]. Lopetuso LR, et al. Harmful effects and potential benefits of anti-tumor necrosis factor (TNF)-α on the liver. Int J Mol Sci 2018;19:2199. [PubMed: 30060508]

[208]. Kavanaugh A, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 2009;60:976–86. [PubMed: 19333944]

[209]. Mease PJ, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50:2264–72. [PubMed: 15248226]

[210]. Mease PJ, et al. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. J Rheumatol 2010;37:1221–7. [PubMed: 20395648]

[211]. Gordon K, et al. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. J Am Acad Dermatol 2006;54:S101–11. [PubMed: 16488320]

[212]. Leonardi CL, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;349:2014–22. [PubMed: 14627786]

[213]. Mease PJ, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385–90. [PubMed: 10972371]

[214]. Mease PJ, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Ann Rheum Dis 2017;76:1550–8. [PubMed: 28473423]

[215]. Szentpetery A, et al. Abatacept reduces synovial regulatory T-cell expression in patients with psoriatic arthritis. Arthritis Res Ther 2017;19:158. [PubMed: 28679449]

[216]. Abrams JR, et al. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. J Clin Invest 1999;103:1243–52. [PubMed: 10225967]

[217]. Abrams JR, et al. Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. J Exp Med 2000;192:681–94. [PubMed: 10974034]

[218]. Mease PJ, et al. Poor prognostic factors in predicting abatacept response in a phase III randomized controlled trial in psoriatic arthritis. Rheumatol Int 2020;40:1021–8. [PubMed: 32356115]

[219]. Coates LC, Helliwell PS. Methotrexate efficacy in the tight control in psoriatic arthritis study. J Rheumatol 2016;43:356–61. [PubMed: 26669913]

[220]. Saurat J-H, et al. Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. Br J Dermatol 2011;165:399–406. [PubMed: 21564071]

[221]. Sakthiswary R, Chan GYL, Koh ET, Leong KP, Thong BYH. Methotrexate-associated nonalcoholic fatty liver disease with transaminitis in rheumatoid arthritis. Sci World J1 2014;2014:823763.

[222]. Adams LA, Angulo P. Treatment of non-alcoholic fatty liver disease. Postgrad Med J 2006;82:315–22. [PubMed: 16679470]

[223]. Rau R, Karger T, Herborn G, Frenzel H. Liver biopsy findings in patients with rheumatoid arthritis undergoing longterm treatment with methotrexate. J Rheumatol 1989;16:489–93. [PubMed: 2473207]

[224]. Ellis CN, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. N Engl J Med 1991;324:277–84. [PubMed: 1986287]

[225]. Ho VC, et al. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: a 2-year cohort study. J Am Acad Dermatol 2001;44:643–51. [PubMed: 11260540]

[226]. Faerber L, et al. Cyclosporine in severe psoriasis. Results of a meta-analysis in 579 patients. Am J Clin Dermatol 2001;2:41–7. [PubMed: 11702620]

[227]. Ure DR, Trepanier DJ, Mayo PR, Foster RT. Cyclophilin inhibition as a potential treatment for nonalcoholic steatohepatitis (NASH). Expert Opin Investig Drugs 2020;29:163–78.

[228]. Geiger JM. Efficacy of acitretin in severe psoriasis. Skin Therapy Lett 2003;8:1–3.7.

[229]. Murray HE, et al. A 12-month treatment of severe psoriasis with acitretin: results of a Canadian open multicenter study. J Am Acad Dermatol 1991;24:598–602. [PubMed: 1827800]

[230]. Karadag AS, et al. The effect of acitretin treatment on insulin resistance, retinol-binding protein-4, leptin, and adiponectin in psoriasis vulgaris: a noncontrolled study. Dermatology 2013;227:103–8. [PubMed: 24021889]

[231]. An J, et al. The acitretin and methotrexate combination therapy for psoriasis vulgaris achieves higher effectiveness and less liver fibrosis. Pharmacol Res 2017;121:158–68. [PubMed: 28414177]

[232]. Kavanaugh A, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. J Rheumatol 2015;42:479–88. [PubMed: 25593233]

[233]. Kavanaugh A, et al. Long-term experience with apremilast in patients with psoriatic arthritis: 5-year results from a PALACE 1-3 pooled analysis. Arthritis Res Ther 2019;21:118. [PubMed: 31077258]

[234]. Rich P, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). J Am Acad Dermatol 2016;74:134–42. [PubMed: 26549249]

[235]. Efficacy and safety of leflunomide in psoriatic arthritis treatment: a single-arm meta-analysis - Dai −. Wiley Online Library; 2019. - International Journal of Rheumatic Diseases -, https://onlinelibrary.wiley.com/doi/abs/10.1111/1756-185X.13599.

[236]. Behrens F, et al. Leflunomide in psoriatic arthritis: results from a large European prospective observational study. Arthritis Care Res 2013;65:464–70.

[237]. Tlacuilo-Parra JA, et al. Leflunomide in the treatment of psoriasis: results of a phase II open trial. Br J Dermatol 2004;150:970–6. [PubMed: 15149511]

[238]. Kaltwasser JP, et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. Arthritis Rheum 2004;50:1939–50. [PubMed: 15188371]

[239]. Nash P, Thaçi D, Behrens F, Falk F, Kaltwasser JP. Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. Dermatology 2006;212:238–49. [PubMed: 16549920]

[240]. Lijnen R, Otters E, Balak D, Thio B. Long-term safety and effectiveness of high-dose dimethylfumarate in the treatment of moderate to severe psoriasis: a prospective single-blinded follow-up study. J Dermatolog Treat 2016;27:31–6. [PubMed: 26088405]

[241]. van de Kerkhof PCM, et al. Quality of life outcomes in adults with moderate-to-severe plaque psoriasis treated with dimethylfumarate (DMF): a post hoc analysis of the BRIDGE study. J Eur Acad Dermatol Venereol 2020;34:119–26. [PubMed: 31465585]

[242]. Belfort R, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–307. [PubMed: 17135584]

[243]. Aithal GP, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135:1176–84. [PubMed: 18718471]

[244]. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med 2017;177:633–40. [PubMed: 28241279]

[245]. Harrison SA, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multi centre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2019;394:2012–24. [PubMed: 31727409]

[246]. Mudaliar S, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145:574–82. e1. [PubMed: 23727264]

[247]. Neuschwander-Tetri BA, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo controlled trial. Lancet 2015;385:956–65. [PubMed: 25468160]

[248]. Younossi ZM, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019;394:2184–96. [PubMed: 31813633]

[249]. Armstrong MJ, et al. Liraglutide efficacy and action in non-alcoholic steatohepatitis (LEAN): study protocol for a phase II multicentre, double-blinded, randomised, controlled trial. BMJ Open 2013;3:e003995.

[250]. Armstrong MJ, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–90. [PubMed: 26608256]

[251]. Mantovani A, Dalbeni A. Treatments for NAFLD: state of Art. Int J Mol Sci 2021;22:2350. [PubMed: 33652942]

[252]. Hoofnagle JH, et al. Vitamin E and changes in serum alanine aminotransferase levels in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2013;38:134–43. [PubMed: 23718573]

[253]. Kharaeva Z, Gostova E, De Luca C, Raskovic D, Korkina L. Clinical and biochemical effects of coenzyme Q(10), vitamin E, and selenium supplementation to psoriasis patients. Nutrition 2009;25:295–302. [PubMed: 19041224]

[254]. Zein CO, et al. Pentoxifylline improves nonalcoholic steatohepatitis: a randomized placebo-controlled trial. Hepatology 2011;54:1610–9. [PubMed: 21748765]

[255]. Van Wagner LB, et al. Pentoxifylline for the treatment of non-alcoholic steatohepatitis: a randomized controlled trial. Ann Hepatol 2011:10:277–86. [PubMed: 21677329]

[256]. Du J, Ma Y-Y, Yu C-H, Li Y-M. Effects of pentoxifylline on nonalcoholic fatty liver disease: a meta-analysis. World J Gastroenterol 2014;20:569–77. [PubMed: 24574727]

[257]. Magela Magalhaes G, et al. Psoriasis and pentoxifylline: a clinical, histopathologic, and immunohistochemical evaluation. Skinmed 2006;5:278–84. [PubMed: 17085994]

[258]. Ogdie A, Grewal SK, Noe MH, et al. Risk of incident liver disease in patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis: a population-based study. J Invest Dermatol 2018;138:760–7. [PubMed: 29104161]

[259]. Roberts KK, Cochet AE, Lamb PB, et al. The prevalence of NAFLD and NASH among patients with psoriasis in a tertiary care dermatology and rheumatology clinic. Aliment Pharmacol Ther 2015;41:293–300. [PubMed: 25521607]

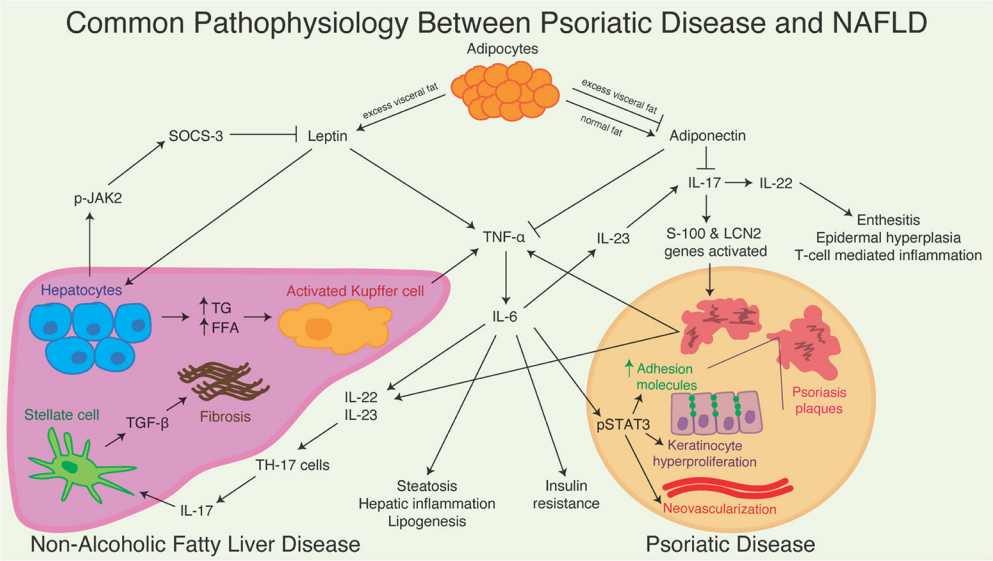

Fig. 1. Shared pathogenesis of non-alcoholic fatty liver disease and psoriatic disease.

The common pathophysiology between PD and NAFLD is primarily driven by adipokine and cytokine inflammatory pathways. Excess visceral fat increases leptin but paradoxically decreases adiponectin which leads to downstream inflammatory processes in both diseases. TNF-alpha and IL-6 are the predominant overlapping factors which ultimately influence IL-22, IL-23, IL-17, and other cytokines to promote inflammation, steatosis and lipogenesis in NAFLD while also promoting an increase in adhesion molecules, keratinocyte hyperproliferation and neovascularization in PD.

NAFLD: non-alcoholic fatty liver disease; PD: psoriatic disease; IL: interleukin; FFA: free fatty acid; TG: triglyceride; TNF: tumor necrosis factor.

Table 1

Psoriatic disease therapeutics and impact on NAFLD .

Drug name	Mechanism of Action	FDA Approval in PsO, PsA, or Both	Level of studies on NAFLD treatment	Potential effect on NA
Ustekinumab **PsA:** McInnes et al., 2013[153] Ritchlin et al., 2014[154] **PsO:** Griffiths et al., 2010[155]; Kimball et al., 2012[156]; Tsai et al., 2011[157]; Papp et al., 2008[158]	Human IgG1k monoclonal antibody against p40 subunit of IL-12 and IL-23	Both	Hypothesis only; may theoretically interrupt pathogenesis	Treatment with ustekinumab led to a significant reduction in levels of TNF-alpha, IL-17a, and IL-6 levels in PsO patients inflammatory cytokines important for pathogenesis of NAFLD/NASH[121].
Tildrakizumab **PsA:** Mease et al., 2021[159] **PsO:** Papp et al., 2015[160]; Reich et al., 2017[161]; Blauvelt et al., 2018[162]; Reich et al., 2020[163]	Humanized IgG1k monoclonal antibody against p19 subunit of IL-23	PsO only	Animal studies	IL-23 blockade prevents NAFLD development in mouse model[120].
Guselkumab **PsA:** Mease et al., 2020[164]; Deodhar et al., 2018[165] **PsO:** Langley et al., 2018[166]; Reich et al., 2017[161]; Blauvelt et al., 2017[167]; Gordon et al., 2015[168]	Humanized IgG1k monoclonal antibody against p19 subunit of IL-23	Both	Animal studies	See above[120].
Risankizumab **PsA:** Ostor et al., 2022[169]; Kristensen et al., 2021[170] **PsO:** Papp et al., 2017[171]; Papp et al., 2021[172]; Blauvelt et al., 2020[173]	Humanized IgG1k monoclonal antibody against p19 subunit of IL-23	Both	Animal studies	See above[120].
Ixekizumab **PsA:** Mease et al., 2017[174], Nash et al., 2017[175]; Mease et al., 2020[176] **PsO:** Griffiths et al., 2015[177]; Blauvelt et al., 2020[173]	Humanized monoclonal IgG4 antibody against IL-17A	Both	Animal studies	In mouse models of NAFLD and NASH, IL-17 blockade decreases hepatic steatosis and hepatic infiltration of inflammatory cells[68,178].
Secukinumab **PsA:** McInnes et al., 2015[179]; Mease et al., 2015[180] **PsO:** Langley et al., 2014[181]; Thaci et al., 2015[182]; Mease et al., 2015[180]; Blauvelt et al., 2016[183]	Human IgG1k monoclonal antibody against IL-17A	Both	Animal studies	See above[68,178].
Brodalumab **PsA:** Mease et al., 2014[184]; Mease et al., 2021[185] **PsO:** Papp et al., 2016[186]; Lebwohl et al., 2015[187] **Both:** Nakagawa et al., 2016[188]	Human IgG2 monoclonal antibody against IL-17RA	PsO only	Animal studies	IL-17A blockade in NASH—HCC mouse model led to decreased tumor size and number of nodules[189]. IL-17A blockade in mouse model decreased the amount of liver injury induced by high fat diet[65].
Infliximab **PsA:** Antoni et al., 2005[190-191]; Kavanaugh et al., 2006[192]	Chimeric monoclonal antibody against TNF-α	Both	Human and animal studies	Infliximab administration shown to reduce inflammation, steatosis, insulin resistance, and

Drug name	Mechanism of Action	FDA Approval in PsO, PsA, or Both	Level of studies on NAFLD treatment	Potential effect on NA
PsO: Menter et al., 2007[193]; Reich et al., 2013[194]; Barker et al., 2011[195]; Chaudhari et al., 2001[196]				fibrosis induced from high fat diet[107-109]. Cross-sectional study showed that TNF-alpha inhibitors may protect against development of fibrosis in patients with PsA[111].
Adalimumab **PsA:** Mease et al., 2005[197]; Genovese et al., 2007[198]; Gladman et al., 2007[199] **PsO:** Saurat et al., 2008[200]; Menter et al., 2008[201]; Gordon et al., 2012[202]	Human IgG1k monoclonal antibody against TNF-α	Both Both	Human and animal studies	In a rat model of NASH, adalimumab did not prevent NASH but did improve some LFTs and NASH histopathology scores[110]. See above[111].
Certolizumab **PsA:** Mease et al., 2014[203]; Gladman et al., 2014[204] **PsO:** Reich et al., 2012[205] **Both:** Dattola et al., 2017[206]	Pegylated Fab fragment of a human monoclonal antibody against TNF-α		Hypothesis only; efficacy of other TNF-α inhibitors on NAFLD	Not specifically studied in NAFLD/NASH but operates via a similar mechanism as Infliximab and Adalimumab which have been shown to be effective in animal models[111,207].
Golimumab **PsA:** Kavanaugh et al., 2009[208]	Human IgG1k monoclonal antibody against TNF-α	PsA only	Hypothesis; efficacy of other TNF-α inhibitors on NAFLD	See above[111,207]
Etanercept **PsA:** Mease et al. 2004[209]; Mease et al., 2010[210] **PsO:** Gordon et al., 2006[211]; Leonardi et al., 2003[212] **Both:** Mease et al., 2000[213]	Dimeric p55 TNF-R-Fc construct	Both	Human studies	Etanercept decreased odds of developing hepatic fibrosis in patients with PsO and NAFLD[112].
Clazakizumab **Both:** Mease et al., 2016 [123]	Humanized IgG1 monoclonal antibody against IL-6	Neither	Hypothesis only; may theoretically interrupt pathogenesis	IL-6 promotes the IL-23/IL-17 pathway by inducing differentiation of CD4+ cells into Th17 cells[84].
No recombinant IL-22 cytokine is currently utilized in PD	Human IL-22-Fc fusion protein	Neither	Animal studies	Therapeutic administration of IL-22 in murine models improves insulin resistance and hepatic steatosis[115,116].
Abatacept **PsA:** Mease et al., 2017[214]; Szentpetery et al., 2017[215] **PsO:** Abrams et al., 1999[216]; Abrams et al., 2000[217] **Both:** Mease et al., 2020[218]	Human cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4)-Ig fusion protein	PsA only	No data	
Methotrexate **PsA:** Coates et al., 2016[219] **PsO:** Saurat et al., 2011[220]; Coates et al., 2016[219]	Inhibition of dihydrofolate reductase	PsO only; often used off-label for PsA	No data	MTX may independently contribute to the development of NAFLD[221-223].
Cyclosporine **PsO:** Ellis et al., 1991[224]; Ho et al., 2001[225]; Faerber et al., 2001[226]	Inhibition of calcineurin	PsO only	Hypothesis; may theoretically interrupt pathogenesis	CsA and non-immunosuppressive cyclophilin analogs can decrease fibrosis and mitochondrial dysfunction– two process important for NASH/ NAFLD development[227].

Drug name	Mechanism of Action	FDA Approval in PsO, PsA, or Both	Level of studies on NAFLD treatment	Potential effect on NA
Acitretin **PsO:** Geiger et al., 2003[228]; Murray et al., 1991[229]	Cytosolic retinoic acid-binding protein (CRABP)	PsO only	Hypothesis; risk factor modification and may theoretically interrupt pathogenesis	Acitretin treatment in patients with PsO improved insulin resistance[230]. Acitretin + MTX treatment in PsO yielded decreased risk of fibrosis when compared with MTX monotherapy[231].
Apremilast **PsA:** Kavanaugh et al., 2015[232]; Kavanaugh et al., 2019[233] **PsO:** Papp et al., 2015[160]; Rich et al., 2015[234]	Inhibition of phosphodiesterase-4 inhibitor	Both	Human studies	ASP9831 (novel PDE4- inhibitor) did not improve any biochemical hepatic parameters in patients with a histological diagnosis of NASH[131].
Lellunomide **PsA:** Dai et al., 2019[235]; Behrens et al., 2013[236] **PsO:** Tlacuilo-Parra et al., 2004[237] **Both:** Kaltwasser et al. 2004[238]; Nash et al., 2006[239]	Inhibition of dihydro-orotate dehydrogenase	Neither	No data	
Dimethyl Fumarate **PsO**: Mrowietz et al., 2017[138]; Lijnen et al., 2016[240]; va de Kerkhof et al., 2020[241]	Augmentation of nuclear factor erythroid 2 related factor 2 (Nrf2) pathway and inhibition of NF-κB pathway	PsO only	No data	

Table 2

NAFLD/NASH Therapeutics and Impact on PD.

Drug Name	Mechanism of Action	Level of studies on PD treatment	Findings in PD
Pioglitazone Sanyal et al., 2010[147]; Belfort et al., 2006[242]; Aithal et al., 2008[243]; Cusi et al., 2016[148]; Musso et al., 2017[244]	Peroxisome proliferator-activated receptors (PPAR)-gamma agonists	Human studies	Meta-analysis: Pioglitazone is an efficacious treatment modality for plaque psoriasis [150]. Meta-analysis: Pioglitazone administration leads to a significant decrease in mean PASI scores and increase in PASI-75 scores[149].
Resmetiron Harrison et al., 2019 [245] Vuppalanchi et al.,. 2021[151]	Thyroid hormone receptor beta (THR-beta) selective agonist	Not studied in PD	
Obeticholic Acid Vuppalanchi et al.,. 2021[151]; Mudaliar et al., 2013[246]; Neuschwander-Tetri et al., 2015[247]; Younossi et al., 2019 [248]	Farnesoid X Receptor (FXR) Agonist	Not studied in PD	
Liraglutide, Semaglutide Vuppalanchi et al.,. 2021 [151]; Armstrong et al., 2013[249]; Armstrong et al., 2016 [250]; Mantovani et al., 2021 [251]	Glucagon Like Peptide 1 (GLP-1) Analog	Human studies	Liraglutide administration in patients PsO and T2DM lead to a significant decrease in PASI scores after 12 weeks[152]
Vitamin E Sanyal et al., 2010[147]; Hoofnagle et al., 2013[252]	Antioxidant	Human studies	In patients with PsA and severe erythrodermic psoriasis, Vitamin E, in combination with Coenzyme Q10 and selenium, showed improvements in reactive oxygen species compared to placebo[253].
Aramchol Vuppalanchi et al.,. 2021[151]	Fatty Acid Synthase Stearoyl-CoA Desaturase (FASN/ SCD1) inhibitors	Not studied in PD	
Pentoxifylline Zein et al., 2011[254] Van Wagner et al., 2011[255] Du et al., 2014[256]	Phosphodiesterase inhibitor	Human studies	No clinical or histological improvement noted with pentoxifylline treatment[257].