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REVIEW ARTICLE

Psoriatic arthritis and obesity: the role of anti-IL-12/IL-23 treatment

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Abstract

Patients with psoriatic arthritis (PsA) have an increased prevalence of obesity, but mechanisms underlying this association remain unknown and it is unclear if obesity is the cause or effect of PsA. For PsA patients, comorbid obesity may influence their clinical response to systemic treatment, and especially targeted immunomodulators such as anti-tumor necrosis factor (TNF)α. Weight gain has also been associated with anti-TNFα treatment. Consequently, modification of the therapeutic approach may be needed for patients with an inadequate response to TNFα inhibitors. In recent years, interleukin (IL)-12/IL-23 inhibitors have entered clinical practice as a new class of drug for the treatment of PsA, with some data suggesting a lower effect of body weight on their effectiveness. Recent findings demonstrate effective and sustained responses in patients with PsA to ustekinumab, an IL-12/IL-23 inhibitor. This narrative review critically discusses the link between PsA, obesity, and response to therapy. The current role of ustekinumab in this setting is also discussed.

Keywords Biological therapy · Interleukin inhibitor · MDA in PsA · Obesity · Psoriatic arthritis · Therapeutic response

Introduction

Psoriatic arthritis (PsA), which has an estimated prevalence of 0.06–0.25% in developed countries, is a chronic inflammatory disease characterized by the involvement of skin, nails, peripheral and axial joints, and enthesis [1]. PsA is often associated with other chronic inflammatory manifestations especially skin psoriasis, with a prevalence reaching 41% [1], leading to the concept of psoriatic disease (i.e., a systemic condition that is not only confined to the skin and musculoskeletal system, but also involves several different organs such as the bowel and the eye).

Nowadays, inflammation is considered to be more than a pathological finding confined to an organ or tissue, but has become a paradigm in which tissue metabolism can interfere thereby determining a pathological loop where the first insult cannot be easily traced. As a result, inflammation is now a hot topic for obesity, which is one of the most common conditions of recent times [2].

According to the World Health Organization [3], obesity is defined as a body mass index (BMI) ≥ 30 kg/m^2. Worldwide obesity has nearly tripled since 1975; in 2016, 39% of adults aged ≥ 18 years were overweight (BMI ≥ 25 and < 30 kg/m^2), and 13% were obese, with a higher frequency in Western countries [3]. Hence, obesity is a major worldwide health problem. Indeed, mathematical modeling has suggested that 51% of the population worldwide will be obese by 2030 [4].

Obesity is associated with a chronic low-grade of inflammation, with studies showing for example a significant increase of many cytokines as well as interleukin (IL)-17 and IL-23 plasma levels in obese women compared with lean individuals [5]. Epidemiological studies have also demonstrated a higher risk of developing obesity in PsA patients, which might be due to common pathophysiological mechanisms [6].

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The interaction between PsA and obesity can be also highlighted by the reciprocal influence which these conditions have on key molecules such as tumor necrosis factor (TNF)α. While it is widely accepted that obesity is associated with poorer therapeutic response to anti-TNFα in psoriasis [7], the effects of obesity on treatment response to anti-TNFα in patients with PsA are less well studied. TNFα inhibitors may induce weight gain in PsA patients [8] and being overweight might reduce their effectiveness [9, 10]. These elements should be considered in treatment selection.

In recent years, IL-12/IL-23 inhibitors have entered clinical practice as a new class of drug for the treatment of PsA [11, 12]. Recent findings demonstrate that IL-12/IL-23 inhibitors show an effective and sustained response in PsA patients without apparently being affected by body weight [13]. This narrative review critically discusses the link between PsA, obesity, and response to therapy. The current role of the IL-12/IL-23 inhibitor, ustekinumab, in this setting is also discussed.

Inflammatory mechanisms in obesity

Adipose tissue was initially considered to be a storage organ for fatty acids without other functions; nowadays, its role as an endocrine organ is globally accepted [14]. In addition to adipocytes, adipose tissue is composed of stromal-vascular cells and leukocytes. Cytokines secreted by adipose tissue, generally named adipokines, are regulated by a complex network of genetic and environmental factors, and obesity is associated with the abundance of macrophages, neutrophils, T cells, B cells, and mast cells in adipose tissue [15]. The milieu created by increased proliferation of immune cells determines major changes in adipokine secretion [16].

Adiponectin is an anti-inflammatory cytokine [2, 17], and low serum levels of adiponectin are frequently reported in patients with obesity or psoriasis. In subjects with inflammatory diseases, high levels of cytokines such as TNFα or IL-6 may further reduce adiponectin synthesis by adipose tissue. Moreover, reduced levels of adiponectin are associated with insulin resistance, impaired vasodilatation, neo-vascularization, and diastolic heart failure [17]. Therefore, it can be hypothesized that adiponectin could exert protective effects in obesity-related metabolic and vascular diseases, presumably due to its anti-inflammatory action.

On the other hand, the concentration of leptin, the main protein secreted by adipose tissue, increases with fat mass and inflammatory activity [18], and conditions characterized by systemic inflammation, such as psoriasis and PsA, can increase leptin synthesis. Moreover, leptin also influences the cardiovascular system via the induction of endothelial dysfunction leading to atherosclerosis [19].

Plasminogen activator inhibitor-1 (PAI-1) is the most important inhibitor of plasminogen activation, and increased levels of circulating PAI-1 are associated with obesity-related abnormalities of hemostasis [2]. Levels of PAI-1 decrease significantly with weight loss, and PAI-1 correlates with all components of the metabolic syndrome (MS); thus, the increased levels of PAI-1 observed in obesity enhance the risk of atherothrombosis [2]. Obesity and MS also appear to be associated with other hemostasis alterations, including enhanced platelet activity [2].

Obesity is also associated with increased secretion of IL-6 by adipose tissue [18]. Therefore, obese individuals show a systemic chronic inflammatory condition with higher hepatic release of acute-phase inflammation mediators, such as C-reactive protein, compared with non-obese individuals [2].

Lastly, TNFα, which is also secreted by adipose tissue, exerts multiple effects on inflammation and metabolism [18]. In PsA patients, TNFα acts as a pro-inflammatory cytokine on the synovial tissue and endothelium. Moreover, it induces insulin resistance and contributes to increased serum levels of atherogenic lipoproteins [20].

Obesity and psoriatic arthritis

Recent findings report a high prevalence of obesity in PsA patients compared with the general population [21, 22]; however, this correlation is not simply due to chronic inflammation in autoimmune diseases. Notably, clinical and epidemiological studies support the correlation between PsA incidence and obesity [23], as discussed below.

The prevalence of obesity was higher in patients with PsA compared with patients with psoriasis without arthritis [24, 25]. Furthermore, obesity in adolescence (i.e., a higher reported BMI at 18 years of age) is a strong risk factor for PsA development during adulthood [26].

Obesity was significantly more frequent in PsA patients than in patients with rheumatoid arthritis (RA) ($p = 0.007$) in a registry of 294 PsA and 1662 RA patients [27]. A case-controlled study, which compared the BMI of patients with PsA ($n = 644$), psoriasis ($n = 448$), RA ($n = 350$), and the general population ($n = 115{,}787$), showed that obesity was more common in patients with PsA than in those with psoriasis, RA, or the general population [28]. Multivariate logistic regression analysis further showed that the odds of obesity were 61% higher in PsA than in psoriasis after adjusting for age, gender, smoking, psoriasis duration, psoriasis area severity index score, and the use of disease-modifying anti-rheumatic drugs, glucocorticoids, and biologics.

Higher BMI levels were associated with an increased incidence of PsA in a large population-based study of 75,395 individuals with psoriasis, of whom 976 developed PsA [29]. Compared with a BMI < 25 kg/m^2, the relative risk (RR) for developing PsA was 1.1, 1.24, and 1.52 for BMIs of 25–29.9 kg/m^2, 30.0–34.9 kg/m^2, and ≥ 35.0 kg/m^2,

respectively (p for trend < 0.001). The association between obesity and the risk of PsA was also demonstrated in a large cohort of US women (n = 89,049), in which 146 incident PsA cases were identified during 1,231,693 person-years of follow-up [30]. Compared with a BMI < 25.0 kg/m^2, the RR for developing PsA was 1.83, 3.12, and 6.46 for BMIs of 25–29.9 kg/m^2, 30–34.9 kg/m^2, and > 35.0 kg/m^2, respectively (p for trend < 0.0001).

Although the epidemiological correlation between PsA and obesity is evident, the underlying mechanisms remain uncertain. Obesity may induce a systemic low-grade inflammation, with an increase of inflammatory cytokines (IL-6, TNFα), and promote the synthesis of leptin and adiponectin, which may contribute to the development of psoriatic disease in susceptible individuals [25]. In an alternative hypothesis, elevated body mass leads to PsA through biomechanical stress, resulting in joint micro-traumas; aberrant response to micro-traumas triggers uncontrolled inflammation resulting in PsA [31]. These two hypotheses are not alternative but may concur to increase the basal level of inflammation in psoriatic disease. Whether obesity is a cause or consequence of PsA requires clarification.

Interestingly, a recent study, which looked at cytokine gene single-nucleotide polymorphisms (SNPs) in 82 patients with psoriasis, found that the SNP rs17782313 had a significant influence on the development of PsA, as well as the presence of obesity [32]. This suggests that specific cytokine gene polymorphisms may influence the occurrence of comorbidities in patients with psoriasis, although larger, prospective studies are needed to confirm this hypothesis.

Influence of obesity on therapeutic response in PsA patients

For patients with PsA, obesity as a comorbidity may influence the clinical response to systemic treatment, and especially the response to anti-TNFα molecules, hence modification of the therapeutic approach may be needed for patients with an inadequate response. The presence of huge fat mass may affect the volume of distribution of an administered drug, as well as its elimination, leading to insufficient dosing and limited efficacy [2, 33]. Moreover, robust clinical evidence from observational studies and daily clinical experience shows that TNFα blockade may be less effective in obese patients and in those with MS, while inhibition of T cell co-stimulation seems not to be influenced [10, 34]. More recently, obesity was shown to be associated with a lower response to anti-TNFα agents in patients with inflammatory diseases, including PsA, suggesting that elevated circulating levels of T helper (Th)17 cells and IL-17 may predict an inadequate therapeutic response to TNFα blockers [35, 36].

In patients with PsA, obesity reduced the response and adherence to TNFα inhibitors and was associated with higher disease activity [37]. Obesity was also shown to be a negative predictor of achieving and maintaining minimal disease activity (MDA) in a prospective study of 270 PsA patients, 135 of whom were obese (BMI > 30 kg/m^2) [38].

Weight loss was found to be associated with an increased rate of MDA achievement for overweight/obese PsA patients who initiated treatment with TNFα blockers [39]. Regardless of diet type, a weight loss of ≥ 5% from baseline predicted the achievement of MDA after 6-month treatment with TNFα inhibitors.

These findings were confirmed in a 10-year study conducted at the University of Toronto PsA Clinic on 557 PsA patients, of whom 36.2% were overweight (BMI 25–30 kg/m^2) and 35.4% were obese (BMI > 30 kg/m^2) [40]. Sustained MDA was achieved by 66.1% of patients overall; however, patients who were overweight or obese were less likely to achieve sustained MDA compared with those of normal weight.

Remarkably, a systematic review, which assessed the association between obesity and control of inflammatory activity in PsA patients on TNFα inhibitors, found that the likelihood of achieving and maintaining MDA was reduced in obese PsA patients and that obesity was associated with higher rates of treatment discontinuation and lower skin response [9]. Therefore, the decreased likelihood of achieving MDA in overweight PsA patients who are treated with TNFα inhibitors should be considered [41].

Influence of biological agents on adiposity

Weight gain has been described during anti-TNFα treatment; however, the actual mechanisms underlying this effect are currently unclear. There are currently two models, which are based either on direct metabolic effects of TNFα inhibitors on adipose tissue [8, 42] or indirect effects on patient lifestyle [43, 44].

Gains in both fat and lean mass were identified following 24-week treatment with TNFα inhibitors, with increases in body weight reported in 75% of psoriasis (n = 20) and 60% of PsA (n = 20) patients [8]. Notably, significant increases in the percentage change in body weight and in fat and lean mass were identified for both patient populations (all $p \leq 0.05$ versus baseline).

Furthermore, a retrospective cohort analysis of patients with chronic plaque psoriasis treated for 6 months with TNFα inhibitors reported a significant mean increase in body weight for etanercept (n = 58) and infliximab (n = 40) (both $p \leq 0.004$ vs. baseline) but not for methotrexate (n = 43) [43].

Approximately 25% of patients treated with TNFα inhibitors had weight gains of between 4 and 10 kg, and the relative risk of gaining ≥ 5 kg of body weight was 4.3 times higher for patients treated with TNFα inhibitors compared with methotrexate.

These effects do not appear to occur with the new generation of biologic therapies. The IL-12/IL-23 inhibitor, ustekinumab ($n = 79$), was not associated with increased BMI or body weight compared with infliximab ($n = 83$) in patients with chronic plaque psoriasis treated over a 7-month period, [45] suggesting that ustekinumab may offer a promising treatment option for PsA patients with obesity.

Possible role of IL-12/IL-23 inhibition in the treatment of PsA patients with obesity

A key role for IL-23 in the pathogenesis of PsA has been proposed. Notably, significantly higher levels of IL-23 were identified in the sera of patients with PsA compared with normal psoriasis [46]. Evidence has also shown connections between IL-23 inflammation pathways in psoriatic skin, bone marrow, and gut with pathological manifestations such as enthesitis, synovitis, and altered bone. For example, dysbiosis of gut microbiota may initiate inflammation in the ileo-colon and trigger IL-23 release and Th17 cell activation and proliferation. In the enthesis, IL-23 release in response to biomechanical stress or trauma at the tendon-insertion site activates Th17 cells promoting the secretion of pro-inflammatory cytokines, including IL-17, IL-22, and TNFα, with resultant inflammation, bone erosion, and pathologic bone formation [47]. IL-23, a pro-inflammatory cytokine, can act on different target cells via either IL-17-dependent or IL-17-independent mechanisms [48]. These networks lead to the recruitment of inflammatory cells within the inflamed tissue.

Subcutaneous adipose tissue from metabolically abnormal, insulin-resistant, obese individuals was found to have a specific CD4+ T cell signature with increased numbers of IL-17 and IL-22–producing cells compared with metabolically normal, insulin-sensitive, obese individuals and lean subjects [49]. Both IL-17 and IL-22 inhibited insulin-mediated glucose metabolism in liver and muscle tissue in vitro [49], suggesting that alterations in adipose tissue lymphocyte function may potentially be linked with metabolic disease.

The pivotal role of pathogenic Th17 cells in obesity with regard to the onset and/or progression of chronic inflammatory diseases has recently been reviewed [50]. It is likely that Th17 cells play a crucial role in the pathogenesis of obesity that is linked to their pro-inflammatory properties and also via their influence on metabolism, which can be modified with a hypercaloric diet. Indeed, a hypercaloric diet has been shown to induce an enrichment of pathogenic Th17 cells in several tissues and can also cause a pronounced decrease of intestinal IL-17/IL-22 secreting RORγt$^+$ Th17 cells [50]. Hence, targeting the Th17 cell subset through the inhibition of IL-23 might improve therapeutic outcomes.

Ustekinumab is the first biological drug specifically targeting IL-12/IL-23 to be approved for the treatment of moderate-to-severe plaque psoriasis, PsA, and Crohn's disease [51]. Ustekinumab exerts its clinical effects by binding p40, the shared subunit of IL-12 and IL-23, thereby interfering with production of the Th1- and Th17-dependent pro-inflammatory cytokines, which are central to the pathology of these inflammatory diseases. Since the IL-23/Th17 axis is a common pathway in both inflammatory-mediated diseases and obesity, targeting IL-23 may have a role in the treatment of obese patients with PsA.

The pivotal, randomized, placebo-controlled, phase III PSUMMIT I trial showed sustained clinical and radiographic benefits in 615 PsA patients with active disease following treatment with ustekinumab 45 mg ($n = 205$) or 90 mg ($n = 204$) compared with placebo ($n = 206$) [52]. Clinical efficacy of ustekinumab was observed after 4-week treatment and was persistently favorable across the 2-year treatment period. At week 100, 56.7–63.6% of patients achieved 20% improvement in American College of Rheumatology (ACR) criteria across the three treatment groups (Fig. 1). Improvements in the clinical signs and symptoms of PsA (including joint and skin disease) alongside inhibition of disease progression were maintained over 2-year treatment with ustekinumab, with no unexpected adverse events. These results demonstrate a favorable risk-benefit profile for ustekinumab in PsA patients with active disease. However, it should be noted that patients ≤ 100 kg generally had numerically higher response rates to ustekinumab than patients with a body weight > 100 kg. Moreover, a post hoc analysis showed higher ACR and Psoriasis Area and Severity Index response rates for patients > 100 kg receiving ustekinumab 90 mg compared with the 45 mg dose [52]. Whether this is due to insufficient serum concentrations of ustekinumab in obese patients receiving ustekinumab 45 mg, remains to be clarified.

The effectiveness of ustekinumab in PsA patients with a high BMI has also been evaluated in "real-life" studies. A high level of satisfaction and good safety profile of ustekinumab were reported in interim analyses of the SUSTAIN trial, a prospective, multi-center, non-interventional study evaluating the long-term efficacy, safety, quality of life, and other patient-reported outcomes of ustekinumab in PsA patients (planned assessment of 400 patients) in a real-life setting [53, 54]. To date, 336 patients from 75 centers have been documented

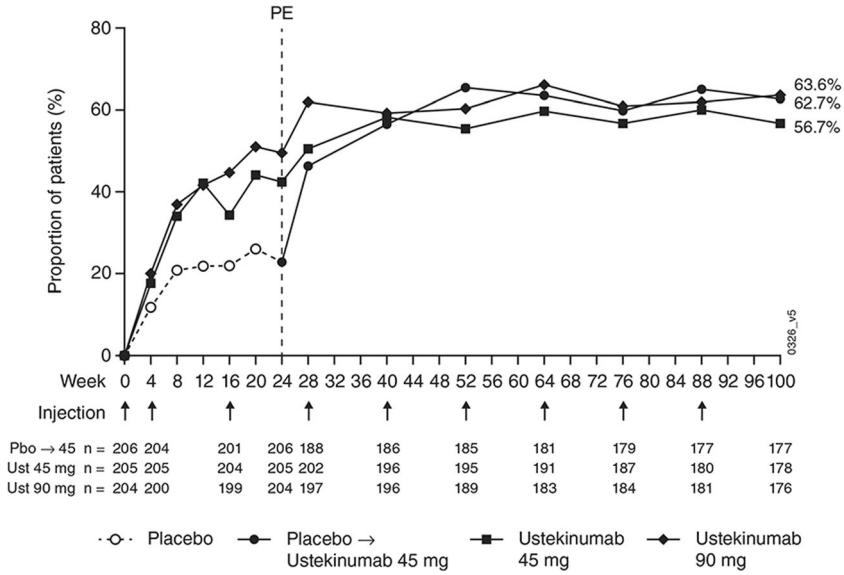

Fig. 1 Percentage of patients achieving 20% improvement in American College of Rheumatology criteria from week 0 to week 100. PE, primary end point; Pbo, placebo; Ust, ustekinumab. Figure reproduced with permission from Kavanaugh et al. 2015 [52]

(mean BMI 30 kg/m^2 at baseline). Compared with baseline, improvements in the mean number of tender and swollen joints were observed after 4- and 76-week treatment with ustekinumab. At week 76, the efficacy and safety of ustekinumab were assessed as "good/very good" by 89.9–90.7% and 98% of treating physicians and patients, respectively. Only 13 ustekinumab-related serious adverse events occurred.

Ustekinumab was also shown to be safe and effective in PsA patients with comorbidities and prior failure on biologic therapies in a real-life clinical setting, with significant improvements in the mean number of tender and swollen joints observed at 24 months (both $p < 0.0001$ vs. baseline) [55].

A separate observational study demonstrated that while ustekinumab was effective in PsA patients with prior biologic exposure, biologic-naïve PsA patients achieved optimal outcomes in terms of treatment persistence and clinical efficacy [13]. At 12 months, biologic-naïve patients had significantly higher ustekinumab retention rates, were less likely to discontinue ustekinumab treatment, and had a significantly greater mean decrease from baseline in the Disease Activity Psoriatic Arthritis score at both 6 and 12 months, compared with patients with prior TNFα-IR exposure.

Ustekinumab was also shown to be effective and safe under conditions of real-world clinical practice in a single-center, observational study of 50 PsA outpatients (28% with BMI > 30 kg/m^2) who used ≥ 3 doses of ustekinumab from March 2015 to March 2017 [56]. Overall, 54% of patients treated with ustekinumab achieved a MDA response, and all items of the Psoriatic Arthritis Impact of Disease questionnaire, which assesses disease impact from the patients' perspective, were significantly lower in patients with MDA compared with non-MDA patients ($p < 0.001$ for all comparisons).

Although these studies did not specifically assess the impact of BMI on clinical outcomes, they do demonstrate ustekinumab is an effective and safe therapeutic treatment for PsA with beneficial outcomes observed even in obese patients. On the other hand, post hoc results from the PSUMMIT I trial suggest that body weight may have an effect on the efficacy of ustekinumab. Therefore, this issue should be addressed in further randomized, controlled trials.

Conclusions

The high prevalence of obesity in patients with PsA represents a complicated situation for physicians. Studies have shown that treatment with anti-TNFα leads to significant increases in body weight in patients with PsA. Furthermore, obesity as a comorbidity in PsA patients may alter their clinical response to systemic treatment, and especially their response to TNFα-blockers. By specifically targeting IL-12/IL-23, ustekinumab interferes with production of the Th1- and Th17-dependent pro-inflammatory cytokines, which are central to the pathology of inflammatory diseases, including PsA. Sustained clinical and radiographic benefits of ustekinumab were demonstrated in the pivotal, phase III PSUMMIT I trial of patients with PsA, and "real-life" studies have confirmed its efficacy and safety in PsA patients with comorbidities and prior failure on biologic therapies, with no apparent effect on body weight during therapy. Whether body weight has an effect on the efficacy of ustekinumab is a controversial issue that remains to be clarified. While randomized, controlled trials are needed to definitively determine its effectiveness and safety, ustekinumab may offer a promising treatment option for PsA patients with obesity.

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