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REVIEW ARTICLE

Biologic and Small-Molecule Therapies for Moderate-to-Severe Psoriasis: Focus on Psoriasis Comorbidities

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Abstract

Psoriasis is a systemic immune-mediated disease associated with an increased risk of comorbidities, such as psoriatic arthritis, cardiovascular disease, metabolic syndrome, inflammatory bowel disease, psychiatric disorders, and malignancy. In recent years, with the advent of biological agents, the efficacy and safety of psoriasis treatments have dramatically improved. Presently, tumor necrosis factor-α inhibitors, interleukin-17 inhibitors, interleukin-12/23 inhibitors, and interleukin-23 inhibitors are approved to treat moderate-to-severe psoriasis. Small-molecule inhibitors, such as apremilast and deucravacitinib, are also approved for the treatment of psoriasis. Although it is still unclear, systemic agents used to treat psoriasis also have a significant impact on its comorbidities by altering the systemic inflammatory state. Data from clinical trials and studies on the safety and efficacy of biologics and small-molecule inhibitors provide important information for the personalized care and treatment for patients with psoriasis. Notably, treatment with interleukin-17 inhibitors is associated with new-onset or exacerbations of inflammatory bowel disease. In addition, great caution needs to be taken when using tumor necrosis factor-α inhibitors in patients with psoriasis with concomitant congestive heart failure, multiple sclerosis, and malignancy. Apremilast may induce weight loss as an adverse effect, presenting also with some beneficial metabolic actions. A better understanding of the characteristics of biologics and small-molecule inhibitors in the treatment of psoriasis comorbidities can provide more definitive guidance for patients with distinct comorbidities.

Key Points

Treatment regimens for patients with psoriasis should be tailored to meet the specific needs based on disease severity, the impact on quality of life, the response to previous therapies, and the presence of comorbidities.

Evidence from clinical trials provides pertinent information regarding the safety and efficacy of biologic agents and small-molecule drugs for psoriasis, which should be integrated into clinical decision making. Furthermore, practical recommendations are necessary regarding first-line systemic therapy options for patients with psoriasis and distinct comorbid conditions.

We provide evidence-based recommendations for the use of psoriasis treatments in patients with distinct comorbidities.

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1 Introduction

Psoriasis is a chronic, inflammatory, immune-mediated, systemic disease affecting approximately 2–3% of the population worldwide [1, 2]. An improved understanding of psoriasis pathogenesis has led to the identification of multiple new therapeutic targets, including anti-tumor necrosis factor (TNF)-α, anti-interleukin (IL)-17, anti-IL-12/23, and anti-IL-23 therapies, which have revolutionized the treatment options for psoriasis [3, 4]. However, no single therapy options work for all patients. Psoriasis is associated with certain comorbid conditions, such as psoriatic arthritis (PsA), cardiovascular disease, metabolic syndrome, inflammatory bowel disease (IBD), psychiatric disorders, multiple sclerosis (MS), and malignancy (Fig. 1) [5]. The shared immunologic and genetic features may in part help explain the epidemiological association between psoriasis and psoriasis-related comorbidities [6, 7]. These comorbid disease conditions often impact the clinical decision to select one therapy over another, and it is important to consider that certain treatments may improve or exacerbate comorbidities of psoriasis [8]. Indeed, biological therapies targeting pro-inflammatory cytokines in the pathogenesis of psoriasis might not only improve skin symptoms but also alter systemic inflammation, hence influencing long-term outcomes of psoriasis comorbidities [9, 10]. Currently, there are four classes of biologic agents approved by the US Food and Drug Administration (FDA) for use in moderate-to-severe psoriasis, including TNF-α inhibitors (etanercept, adalimumab, infliximab, certolizumab pegol), anti-IL-12/23 agents (ustekinumab), anti-IL-17 agents (secukinumab, ixekizumab, brodalumab), and anti-IL-23 agents (guselkumab, tildrakizumab, risankizumab) (Fig. 1) [11]. Although not currently approved by FDA, we also discussed the treatment recommendation of bimekizumab, which is a monoclonal antibody that selectively neutralises IL-17A and IL-17F [12].

In addition, our review included data on small-molecule inhibitors, including oral phosphodiesterase 4 inhibitor (apremilast) and tyrosine kinase 2 inhibitor (deucravacitinib). Importantly, each biologic agent and small-molecule inhibitor has its own advantages and limitations for the

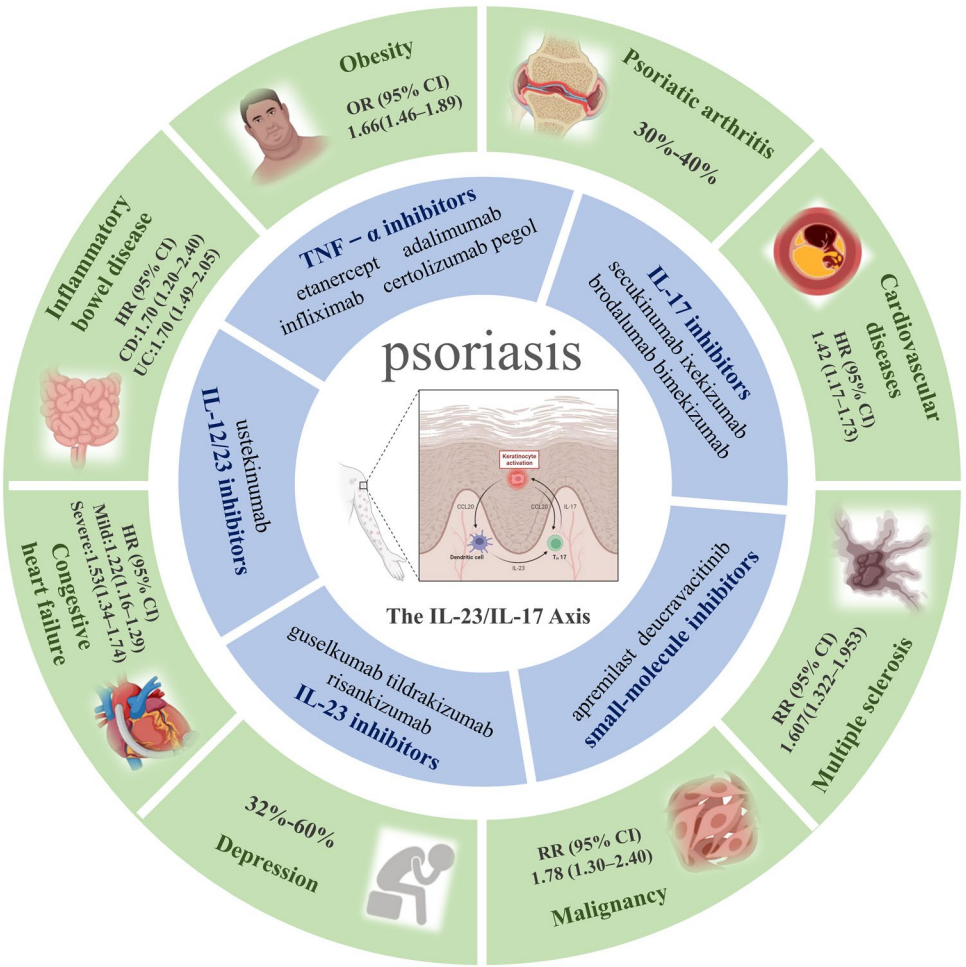

Fig. 1 Summary of systemic treatment options and comorbidities in psoriasis. The inner ring depicts current biologic and small-molecule inhibitors for psoriasis, the outer ring depicts the strength of the association between psoriasis and comorbidities. *CI* confidence interval, *HR* hazard ratio, *IL* interleukin, *OR* odds ratio, *RR* relative risk, *TNF* tumor necrosis factor, *UC* ulcerative colitis

treatment of psoriasis [13]. As the available therapeutic targets for psoriasis increased, psoriasis-related comorbidities may complicate the choice of psoriasis treatment. Dermatologists should be aware of the presence of these comorbidities when formulating an individualized treatment plan for a patient with psoriasis [14]. The review focuses on the possible effects of biologic agents and small-molecule inhibitors used to treat psoriasis on psoriasis comorbidities and provides insight into selecting appropriate biologic therapy options for patients with psoriasis with distinct comorbidities.

2 PsA

Psoriatic arthritis, which is characterized by dactylitis and enthesis, is closely associated with psoriasis. Up to 30–40% of patients with psoriasis will develop PsA, with an average of 10 years between psoriasis and PsA [15]. The overlapping of genetic variations and inflammatory mediators involved in psoriasis and PsA implies a common pathogenic mechanism between the two diseases [16].

2.1 TNF-α Inhibitors

The therapeutic effect of TNF-α inhibitors in PsA has been the subject of many clinical trials. In a randomized controlled trial (RCT), patients with psoriasis and PsA receiving etanercept experienced significant clinical improvement at 12 weeks, including Psoriatic Arthritis Response Criteria, American College of Rheumatology 20% response criteria (ACR20), and the Psoriasis Area and Severity Index (PASI) [17]. Mease et al. compared the efficacy of etanercept versus methotrexate in PsA at week 24, and found that etanercept monotherapy sustained superior efficacy than methotrexate monotherapy for ACR20 response at week 24 (etanercept: 60.9%, methotrexate: 50.7%; $p = 0.029$) [18]. Similarly, other anti-TNF-α agents (adalimumab, infliximab, and certolizumab) also demonstrated a significant impact on the signs and symptoms in patients with PsA and have been approved for clinical use [19–21]. In a network meta-analysis of 46 RCTs comparing the efficacy of various systemic therapies for active PsA, anti-TNF therapies ranked highest in the ACR response [22]. Therefore, we recommend anti-TNF-α agents as the first-line option (Table 1).

Table 1 Treatment recommendations for patients with psoriasis with distinct comorbidities

Patients with psoriasis with psoriatic arthritis	First line: TNF inhibitors, ixekizumab, secukinumab, guselkumab, risankizumab Second line: brodalumab, bimekizumab, apremilast Third line: tildrakizumab, ustekinumab, deucravacitinib
Patients with psoriasis with obesity	First line: IL-17 inhibitors, ustekinumab Second line: IL-23 inhibitors, apremilast Third line: TNF inhibitors
Patients with psoriasis with inflammatory bowel disease	First line: adalimumab, infliximab Second line: certolizumab pegol (for CD), ustekinumab, IL-23 inhibitors (for CD) Third line: apremilast (for UC) Avoid: IL-17 inhibitors
Patients with psoriasis with cardiac diseases	First line: TNF-α inhibitors Second line: IL-17 inhibitors, IL-23 inhibitors, apremilast Third line: ustekinumab
Patients with psoriasis with congestive heart failure	First line: IL-17 inhibitors, IL-23 inhibitors, ustekinumab TNF inhibitors: Avoid in NYHA class III and IV Avoid in patients with ejection fraction <50%
Patients with psoriasis with depression	First line: IL-23 inhibitors Second line: secukinumab, ixekizumab, ustekinumab Third line: TNF inhibitors
Patients with psoriasis with multiple sclerosis	First line: IL-17 inhibitors Second line: ustekinumab Third line: IL-23 inhibitors Avoid: TNF inhibitors
Patients with psoriasis with malignancy	First line: IL-17 inhibitors, IL-23 inhibitors Second line: ustekinumab Avoid: TNF inhibitors

CD Crohn's disease, *IL* interleukin, *NYHA* New York Heart Association, *TNF* tumor necrosis factor, *UC* ulcerative colitis

2.2 IL-17 Inhibitors

A phase III RCT for secukinumab reported that secukinumab 150 or 300 mg remarkably improved the signs and symptoms of axial PsA versus placebo [23]. Additionally, secukinumab was tested in two long-term clinical trials for patients with active PsA and demonstrated sustained inhibition of radiographic progression through 104 weeks of therapy [24, 25]. A phase III RCT evaluating secukinumab versus adalimumab in patients with psoriasis with concomitant PsA reported that secukinumab has a higher PASI 100 response (secukinumab: 39.1%, adalimumab: 23.8%; $p = 0.0136$); responses to ACR20 were similar (secukinumab: 76.4%, adalimumab: 68.3%; $p = 0.1752$) [26]. In a phase III RCT to assess the safety and efficacy of ixekizumab in biologic-naïve patients with active PsA, ixekizumab led to a significant improvement in disease activity and physical function at week 24 [27]. Another phase III RCT for ixekizumab demonstrated an improvement in health-related quality of life and work productivity through 52 weeks of treatment [28]. An open-label head-to-head study compared the efficacy of ixekizumab versus adalimumab in patients with psoriasis with comorbid PsA for 24 weeks as measured by ACR50 and PASI 100. Data suggested that ixekizumab was superior for PASI 100 (ixekizumab: 60%, adalimumab: 47%; $p = 0.001$) but non-inferior for ACR50 (ixekizumab: 51%, adalimumab: 47%), with fewer serious adverse events (adalimumab: 8.5%; ixekizumab: 3.5%) [29]. Similarly, in a 52-week multicenter study (SPIRIT), a significantly higher proportion of patients treated with ixekizumab versus adalimumab achieved PASI 100 (64% vs 41%), but there was no difference in ACR50 (49.8% vs 49.8%) at week 52 [30]. Therefore, secukinumab and ixekizumab are also recommended as first-line drugs for patients with PsA.

Brodalumab, although not currently approved for PsA, has shown good results in several studies. A integrative analysis of two phase III RCTs studying brodalumab in patients with PsA indicated that brodalumab treatment led to improvements in signs and symptoms of PsA assessed by ACR20 as compared with placebo (45.8% and 47.9% for 140 mg and 210 mg, respectively, and 20.9% for placebo) [31]. Similarly, a higher proportion of patients achieved patient-reported improvements in the brodalumab group versus placebo at weeks 24 in a phase II study [32]. In a subgroup analysis ($n = 928$) comparing brodalumab and ustekinumab in patients with psoriasis with comorbid PsA status, brodalumab was more effective in treating PsA than ustekinumab, including quality-of-life improvement and complete skin clearance [33]. Thus, brodalumab was considered to be second-line treatment.

With regard to bimekizumab, in a phase IIb RCT (BE ACTIVE; $n = 206$) in patients with active PsA for 48 weeks, significantly higher proportions of patients experienced ACR50 response in all groups receiving bimekizumab (24–46%) compared with the placebo group (7%) at week 12, with fewer adverse events (bimekizumab: 41%; placebo: 57%) [34]. The treatment efficacy in skin and joint outcomes was sustained for up to 48 weeks [34]. Merola et al. compared the efficacy of bimekizumab versus placebo in patients with PsA who had previously responded inadequately to TNF inhibitors, and reported significant improvements in the primary endpoint (ACR50; 43.4% vs 6.8%; $p < 0.001$) at week 12 [35]. The open-label extension study of BE ACTIVE assessed the long-term efficacy and tolerability of bimekizumab in patients with PsA up to a total of 152 weeks. Patients in the open-label extension maintained treatment response and improvements in pain, fatigue, physical function, and health-related quality of life over 3 years [36]. Ongoing phase III studies of bimekizumab in PsA will help to better understand its therapeutic effects. At this time, we recommend bimekizumab as a second-line option for patients with PsA.

2.3 IL-23 Inhibitors

Guselkumab was tested in two phase III clinical trials for patients with PsA, and did demonstrate robust efficacy in the signs and symptoms of PsA [37, 38]. Sweet et al. found that the serum protein levels of Th17 effector cytokines (IL-17A and IL-17F) in patients with active PsA were decreased after guselkumab or ustekinumab treatment, but the reductions in the guselkumab group were greater than that in ustekinumab-treated patients [39]. In two phase III RCTs (KEEPsAKE 1 AND 2; $n = 964/467$), risankizumab has been shown to significantly improve key disease outcomes (ACR20/50/70, PASI 90) versus placebo, and was well tolerated in patients with PsA [40, 41]. Thus, we recommend guselkumab and risankizumab as first-line treatments.

In a phase IIb RCT ($n = 391$), obviously higher ACR20 response rates were identified in patients receiving tildrakizumab versus placebo (tildrakizumab: 71.4–79.5%, placebo: 50.6%; all $p < 0.01$). However, tildrakizumab treatment did not demonstrate a benefit in dactylitis and enthesitis, and adverse events occurred in 64.5% of patients [42]. Phase III trials of tildrakizumab in patients with PsA are still underway. At this time, we recommend tildrakizumab as a third-line option for patients with PsA.

2.4 IL-12/23 Inhibitors

In two phase III RCTs, more patients receiving ustekinumab achieved ACR20 response versus placebo at week 24, and the treatment effect was sustained through week 52 [43, 44]. Another phase III RCT explored the treatment benefits of ustekinumab in PsA at 12 weeks and reported a significant improvement in all study measures [45]. In particular,

the efficacy of ustekinumab on skin symptoms appears to be better than that on joint inflammation. Siebert et al. found that the C-reactive protein levels in serum samples, but not the levels of IL-17A or IL-17F, were significantly decreased after ustekinumab treatment in patients with PsA [46]. In a case series, seven patients with psoriasis experienced new-onset or worsening PsA after conversion from a TNF-α inhibitor to ustekinumab [47]. Bonifati and Graceffa reported that five patients who discontinued ustekinumab experienced a remission of joint inflammation after reinstituting TNF-α inhibitor treatment, suggesting TNF-α inhibitors had a higher degree of effectiveness than ustekinumab [48]. As ustekinumab is more effective in treating skin diseases than arthritis, it is considered a third-line treatment in patients with PsA.

2.5 Small-Molecule Inhibitors

Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4, is approved by the FDA to treat patients with active PsA [49]. A phase IIIb RCT compared apremilast monotherapy ($n = 110$) and placebo ($n = 109$) in biological-naïve patients with PsA for 52 weeks [50]. Significantly higher proportions of patients receiving apremilast achieved the ACR20 response versus placebo (apremilast: 38.2%, placebo: 20.2%; $p = 0.004$) at week 16, and clinical improvements were sustained through 52 weeks with continued apremilast treatment [50]. Two other phase III RCTs for apremilast in active PsA also demonstrated clinically meaningful improvements in signs, symptoms, physical function, and multiplicity-controlled secondary endpoints [51, 52]. Apremilast is effective in treating PsA, and we recommend apremilast as a second-line treatment.

Deucravacitinib is an oral selective tyrosine kinase 2 inhibitor. In a phase II RCT ($n = 203$), a significantly higher ACR20 was observed with deucravacitinib compared with placebo (52.9% and 62.7% for 6 mg and 12 mg, respectively, and 31.8% for placebo) [53]. These results suggest that deucravacitinib is a promising treatment option for PsA. Further investigations are required to confirm the efficacy of deucravacitinib for PsA. At this time, we consider deucravacitinib to be a third-line option.

3 Obesity

The bidirectional association between obesity and psoriasis has been confirmed in multiple studies. First of all, a higher prevalence of obesity has been observed in patients with psoriasis compared with the general population. Armstrong et al. performed a random-effects meta-analysis of 16 observational studies and found that patients with psoriasis have a higher risk of being obese compared with patients without psoriasis (odds ratio [OR] 1.66; 95% confidence interval [CI] 1.46–1.89) [54]. In particular, severe psoriasis showed an increased odds of obesity compared with patients with mild psoriasis (mild, OR 1.46; 95% CI 1.17–1.82; severe, OR 2.23; 95% CI 1.63–3.05). In addition, the impact of weight gain is associated with an increased incidence of developing psoriasis. In a large longitudinal study enrolling 33,734 individuals, obese people have 1.87 times the odds of having psoriasis compared with normal-weight individuals. Moreover, there is a substantially increased risk of psoriasis for people with a long-term weight gain > 10 kg compared with being weight stable (relative risk [RR] 1.72; 95% CI 1.15–2.58) [55].

3.1 TNF-α Inhibitors

Infliximab in the therapy of psoriasis is dosed based on weight (5 mg/kg). Petridis et al. explored the impact of body mass index (BMI) on the treatment response and quality-of-life improvement in patients with psoriasis treated with infliximab. Through 1 year of treatment, infliximab significantly improved PASI 75 response and Dermatology Life Quality Index scores in patients with psoriasis, independent of baseline BMI [56]. In the diet-induced obesity animal model, infliximab led to a reduction in the levels of blood glucose and insulin, and restored glucose homeostasis [57]. Surprisingly, patients with psoriasis with concomitant overweight or obesity are more likely to sustain the long-term response to infliximab than patients with normal weight for at least 5 years in a real-world study [58]. The dose of etanercept, adalimumab, and certolizumab pegol in the therapy of psoriasis is fixed, and their efficacy and safety are impaired by obesity. A retrospective study investigated the influence of obesity on the long-term efficacy of etanercept for psoriasis. Data suggested that obesity (BMI ≥ 30 kg/m^2) led to a reduction in etanercept efficacy compared with healthy or overweight patients [59]. According to the data of the APHRODITE trial, significantly greater proportions of patients with psoriasis after adalimumab treatment achieved a PASI 50 response in healthy or overweight patient versus obese groups (79% vs 58%, $p = 0.02$) [60]. Similarly, Prussick et al. reported that normal-weight or overweight patients had higher PASI 75 response rates with adalimumab versus obese patients (normal: 85.0%; overweight: 85.7%; obese: 61.3%) [61]. A pooled analysis of 33 clinical trials explored the role of BMI on the risk of adverse events in 8747 patients following certolizumab pegol therapy. The serious infectious events were observed more frequently in people with a BMI >35 kg/m^2 as compared with patients with normal weight [62].

It is also noteworthy that some studies have shown that TNF-α therapies were significantly associated with weight gain. In a cross-sectional study ($n = 191$), patients with

psoriasis gained an average weight of 1.6 kg (2.1%) after 1 year of infliximab treatment compared with baseline weight, mainly in patients with severe psoriasis [63]. As well, in a cross-sectional study of 191 patients with psoriasis, infliximab treatment was associated with severe weight increments [63]. Saraceno et al. performed a retrospective analysis and reported that patients with psoriasis using TNF-α inhibitors experienced an obvious increase in their body weight and BMI at week 24 compared with the control [64]. Similarly, in a meta-analysis comparing the impact of various biologics for psoriasis on the change in body weight and BMI, patients taking TNF-α inhibitors had increases in body weight and BMI more than those on conventional systemic treatments [65]. Tumor necrosis factor-α inhibitors are considered third line for obese patients with psoriasis owing to the potential risk of weight gain with this class of drugs.

3.2 IL-12/23 Inhibitors

In contrast to anti-TNF-α agents, patients with psoriasis initiated on ustekinumab did not experience an increase in their body weight or BMI in a prospective cohort study [66]. In particular, ustekinumab in the treatment of psoriasis is also weight dosed. The patients with body weight <100 kg were administered with the 45-mg dose whereas patients with body weight >100 kg were administered with the 90-mg dose [67]. Overall, because ustekinumab is weight adjusted, we recommend this drug as the first-line treatment.

3.3 IL-17 Inhibitors

Interleukin-17 inhibitors are highly effective agents independent from body weight. In a summary analysis of three RCTs evaluating the impact of body weight on the treatment efficacy of ixekizumab in patients with psoriasis, ixekizumab showed similar degrees of effectiveness in various weight groups [66]. However, in a phase II dose-ranging study, higher PASI 75 responses rates were sustained in patients with psoriasis weighed < 90 kg than those weighing ≥ 90 kg [68]. Based on the pooled analysis of three phase III studies (FIXTURE, ERASURE, and SCULPTURE), secukinumab treatment led to a decreasing trend in body weight at a follow-up of 52 weeks [69]. Babino et al. presented a case of patient with psoriasis affected by morbid obesity who was treated with secukinumab and, after 48 weeks of the treatment, experienced significant improvement in skin symptoms and metabolic parameters [70]. Likewise, compared with obese patients with psoriasis, normal-weight patients treated with brodalumab had higher PASI 75 and PASI 90 responses at week 52 in a phase III RCT [71]. Here, we recommend anti-IL-17 agents as the first-line treatment choice.

3.4 IL-23 Inhibitors

The weight-related data regarding the efficacious anti-IL-23 agents are still sparse, but they are promising therapeutic approaches for obese patients with psoriasis nonetheless. A post hoc analysis of two clinical trials (n = 837/992) evaluated the efficacy of guselkumab in patients with psoriasis grouped by different body weights. Guselkumab was highly efficacious for psoriasis regardless of patient weight [72]. In a real-life study, after guselkumab treatment, the levels of PASI scores in obese and non-obese patients with psoriasis decreased to a similar extent, though the baseline PASI score was higher in obese patients than in non-obese patients [73]. Ruiz-Villaverde et al. reported a case of an obese patient with psoriasis who achieved a successful and sustained response through 52 weeks with risankizumab [74]. Taken together, we also recommend anti-IL-23 agents as second-line therapy.

3.5 Small-Molecule Inhibitors

In several clinical trials for psoriasis (ESTEEM1/2 and PALACE3), apremilast has been shown to reduce body weight and increase insulin sensitivity, suggesting some beneficial metabolic actions [51, 75]. Malara et al. evaluated the real-world effectiveness of apremilast in patients with psoriasis and reported a significant improvement in PASI and Dermatology Life Quality Index scores, irrespective of their weight [76]. Considering the potentially advantageous effect on weight loss, we recommend apremilast as the second-line option for patients with obesity and psoriasis.

4 IBD

Both IBD and psoriasis are chronic inflammatory diseases, and there is a significant association between IBD and psoriasis. The prevalence of psoriasis in patients with Crohn's disease (CD) was 9.6%, whereas the prevalence was 2.2% in the general population. Likewise, the prevalence of CD was 0.5% in patients with psoriasis but only 0.2% in control groups. [77]. Similar trends occur with ulcerative colitis (UC) [78]. In patients with psoriasis, the OR of CD and UC were 1.70 (CI 1.20–2.40) and 1.75 (CI 1.49–2.05), respectively [79]. The shared immunologic and genetic features have been observed in psoriasis and active CD and UC, and treatments used for psoriasis were also used for IBD [80].

4.1 TNF-α Inhibitors

Adalimumab and infliximab have been approved by the FDA for patients with UC and CD, and certolizumab pegol have been approved for the treatment of CD [81]. In a large

real-life study, patients with CD receiving long-term therapy of infliximab experienced a sustained clinical benefit through almost 5 years of follow-up, with a low incidence of hospitalization or surgery [82]. In two RCTs, infliximab maintenance therapy after resective intestinal surgery was effective for preventing CD recurrence for more than 1 year [83, 84]. For patients with moderate-to-severe active UC, significantly higher proportions receiving infliximab 5 mg or 10 mg achieved a clinical response at week 54, defined as a Mayo score reduction of at least 3 points, compared with placebo (5 mg: 45%, 10 mg: 44%, placebo: 20%; $p < 0.001$) [85].

In the CHARM trial ($n = 854$), adalimumab is more effective in maintaining clinical remission in patients with CD than placebo through 56 weeks (adalimumab 40 mg weekly: 41%, placebo: 12%; $p < 0.001$) [86]. In several long-term studies assessing the treatment benefits of adalimumab, adalimumab was effective for maintaining clinical response and remission in patients with CD for up to 4 years, with no new safety signals reported [87, 88]. The treatment effect of adalimumab was also observed in UC. In an RCT, adalimumab induced clinical remission in 18% of patients with active UC at week 8, compared with 9.2% in the patients receiving placebo ($p = 0.031$) [89]. In particular, adalimumab treatment significantly reduced the incidence of hospitalization and surgery and indirect costs in patients with CD [90, 91] and patients with UC [92]. Furthermore, adalimumab appears to be a safe and clinically beneficial alternative for patients with CD and UC who have not responded to infliximab treatment or cannot tolerate infliximab [93, 94].

In an RCT ($n = 930$), certolizumab pegol maintenance therapy led to a maintained response and remission in patients with active CD who had a response to induction therapy of certolizumab pegol compared with patients switching to placebo (certolizumab pegol: 63%, placebo: 36%; $p < 0.001$) [95]. Another RCT evaluating the efficacy outcomes and safety of certolizumab pegol in patients with CD up to 7 years demonstrated certolizumab pegol to be well tolerated for CD, with sustained remission in some patients as long as 7 years [96]. However, in two RCTs, certolizumab pegol did not meet statistical significance in maintaining remission compared with placebo, although the response rate was improved [97, 98]. In regard to UC, a small and noncontrolled study suggested limited or no efficacy for certolizumab pegol in patients with active UC [99].

Roughly speaking, adalimumab and infliximab showed similar degrees of treatment effectiveness in CD or UC, whereas certolizumab pegol appeared to be less effective in patients with CD. Therefore, we recommend adalimumab and infliximab as the first-line treatments for patients with CD or UC and certolizumab pegol as the second-line choice for CD.

Although safe, etanercept does not show the same efficacy as other TNF-α inhibitors in the therapy of CD. An RCT determining the efficacy and safety of etanercept in patients with active CD indicated that etanercept 25 mg was safe, but not effective for the treatment of patients with CD in the primary study endpoint, Crohn's Disease Activity Index score (etanercept: 39%, placebo: 45%; $p = 0.763$) [100]. It should be noted that etanercept treatment might induce exacerbation of CD. In a nationwide cohort study ($n = 17{,}018$), etanercept treatment led to a potential risk of being diagnosed with CD and UC compared with an unexposed cohort (adjusted hazard ratio [HR] 2.0 [CI 1.4–2.8] and 2.0 [CI 1.5–2.8], respectively) [101]. Several studies also presented the cases of CD occurring in patients with psoriasis following a course of etanercept treatment [102, 103].

4.2 IL-12/23 Inhibitors

Ustekinumab was approved by the FDA to treat patients with CD and UC in 2016 and 2019, respectively, after phase III RCTs demonstrated an effective clinical response and remission [104]. Patients with active CD receiving ustekinumab achieved a higher induction response compared with placebo at 6 weeks. Subcutaneous ustekinumab was efficacious for maintaining remission in patients with active CD who had a response to induction therapy through 5 years [104]. Ustekinumab therapy also provided patients with CD with a significant improvement in quality of life and histologic disease activity [105, 106]. Similarly, a pivotal phase III UNIFI trial studying ustekinumab in patients with UC indicated that ustekinumab maintained a superior efficacy versus placebo in clinical response and endoscopic outcomes [107]. However, a real-world study comparing ustekinumab and adalimumab reported that higher rates of induction response and remission were noted in the adalimumab-treated patients than the ustekinumab groups (clinical response: 73.2% vs 50%; remission: 44.3% vs 27.7%) [108]. In a network meta-analysis comparing the efficacy of different first-line agents for patients with active UC, infliximab showed a superiority over ustekinumab in the induction of clinical remission and endoscopic improvement [109]. Overall, ustekinumab should be recommended as a second-line agent for the co-occurrence of psoriasis and IBD.

4.3 IL-17 Inhibitors

A phase IIA RCT explored the efficacy and safety of secukinumab in patients with active CD. Secukinumab was ineffective in treating CD, and higher rates of adverse outcomes were noted in patients taking secukinumab compared with placebo [110]. Based on the safety data of ten phase II/III clinical studies, a pooled analysis reported nine cases of new-onset or exacerbations of IBD in patients with psoriasis

taking secukinumab, compared with one in patients taking etanercept [111]. Two phase III RCTs (UNCOVER-2 and UNCOVER-3) of ixekizumab reported 11 cases of IBD (seven UC and four CD) compared with zero in the placebo-treated patients [112]. Brodalumab 210 mg, 350 mg, or 700 mg were tested in a phase II RCT ($n = 212$) for moderate-to-severe CD and did not demonstrate any benefit compared with placebo, and led to several cases of worsening CD [113]. The association between IL-17 inhibitors and the potential risk of IBD exacerbation was also documented in several case reports. Haidari et al. reported a case of asymptomatic CD in patients with psoriasis following secukinumab treatment [114]. Johnston and Veettil presented a case of a patient with psoriasis who developed UC during treatment initiation with secukinumab [115]. Mu et al. described a patient with chronic plaque psoriasis who manifested CD after treatment with ixekizumab, with no recurrence of clinical disease after stopping ixekizumab treatment [116]. Another case report also presented a patient with psoriasis who was treated with ixekizumab and after 12 weeks of the induction period developed diarrheal illness and rectal bleeding [117]. Marin et al. reported a case of acute self-limited UC occurring in a patient treated with ixekizumab for psoriasis, and the colitis was quickly resolved after treatment withdrawal [118]. For patients with psoriasis and IBD, anti-IL-17 agents should be avoided.

4.4 IL-23 Inhibitors

Preliminary studies investigating anti-IL-23 agents for the therapy of CD demonstrated encouraging data. In a phase II RCT ($n = 309$), guselkumab led to significant improvements in clinical and endoscopic response in patients with moderately to severely active CD at week 12 versus placebo [119]. In two case reports of concomitant psoriasis and CD, patients were successfully treated with guselkumab after not responding to infliximab or ixekinumab therapy [120, 121]. After 12 weeks, patients with active CD treated with intravenous risankizumab showed a higher rate of clinical remission than did those receiving placebo in a phase II RCT (risankizumab: 31%, placebo: 15%, $p = 0.0489$) [122]. In an open-label extension study, risankizumab maintenance therapy was well tolerated and sustained clinical remission (> 71%) and endoscopic response (> 42%) up to 184 weeks [123]. More recently, phase III RCTs (ADVANCE and MOTIVATE) evaluated the efficacy and safety of intravenous risankizumab as induction therapy in patients with moderately to severely active CD. In both trials, risankizumab treatment (600 and 1200 mg) resulted in early symptom control at week 4, and endoscopic evidence of improvement of the mucosa at week 12, with no new safety risks identified [124]. Subsequently, the efficacy of continuing subcutaneous risankizumab as maintenance therapy was assessed in the phase III FORTIFY trial. Significantly greater clinical remission and endoscopic response rates were identified in patients treated with risankizumab compared with placebo [125]. Thus, IL-23 inhibitors are considered second-line treatments for CD. There are no published studies of IL-23 inhibitors for UC.

4.5 Small-Molecule Inhibitors

Danese and Peyrin-Biroulet conducted a phase II RCT for apremilast in patients with active UC. A higher proportion of patients who achieved clinical remission were identified in patients treated with apremilast 30 mg versus placebo (apremilast: 31.6%, placebo: 12.1%; $p = 0.01$) at week 12 [126]. Furthermore, apremilast treatment significantly reduced C-reactive protein and fecal calprotectin compared with the placebo group [126]. At this time, we recommend apremilast as a third-line option for patients with psoriasis with concomitant with UC. Animal models of colitis have shown that phosphodiesterase 4 inhibitors are beneficial, but clinical data of apremilast on CD are not available at present [76].

A number of studies have shown that tyrosine kinase 2 regulates signaling and functional responses downstream of IL-12, IL-23, and type I interferon receptors that are involved in IBD pathophysiology [127, 128]. In the anti-CD40 antibody-induced colitis model, treatment with deucravacitinib dose-dependently protected mice from histologically evident colitis [129]. Clinical trials of deucravacitinib are ongoing in UC (NCT03934216) and CD (NCT03599622).

5 Cardiovascular Diseases

There is growing evidence to support an association between having psoriasis and an increased incidence of major adverse cardiovascular events (MACE), a composite endpoint including myocardial infarction, stroke, and cardiovascular mortality [130, 131]. In a population-based cohort study, the risk of MACE was higher in patients with severe psoriasis compared with unexposed controls (HR 1.42; CI 1.17–1.73) [132].

5.1 TNF-α Inhibitors

A number of studies have shown that treatment of psoriasis with TNF-α inhibitors may decrease the risk of cardiovascular comorbidities. Wu et al. assessed the major cardiovascular event risk in patients with psoriasis receiving TNF-α inhibitors ($n = 9148$) compared with methotrexate ($n = 8581$), and reported that TNF-α inhibitors users had a reduced frequency of cardiovascular events compared with methotrexate (1.45% vs 4.09%; $p < 0.01$) [133]. Moreover, treatment with TNF-α inhibitors leads to an 11% reduction

in the risk of cardiovascular event for every 6 months of cumulative exposure [133]. In a retrospective cohort study of patients with psoriasis, the HR for MACE for patients with psoriasis initiated on TNF-α inhibitors compared with those receiving topical agents was 0.80 (95% CI 0.66–0.98) [134]. Similarly, in a secondary analysis determining the myocardial infarction risk in patients with psoriasis, the use of TNF-α inhibitors for patients with psoriasis was associated with a significant lower risk of myocardial infarction compared with topical therapy (HR 0.27; CI 0.11–0.67) [135]. In a nationwide cohort study investigating the risk of MACE in patients with PsA receiving therapy with different classes of biologics, the risk of MACE was significantly greater with IL-12/23 and IL-17 inhibitors than TNF inhibitors [136]. As TNF-α inhibitors exert a cardioprotective effect, these drugs are considered first-line systemic agents in patients with psoriasis with cardiovascular risk factors.

5.2 IL-12/23 Inhibitors

In the case of IL-12/23 inhibitors, briakinumab reported safety concerns of an increased risk of MACE during the initial analyses, which led to trial discontinuation in 2011 [137]. Briakinumab is no longer under development in any indication. Regarding ustekinumab, a case-time-control study for patients with psoriasis with a high cardiovascular risk found a significantly increased risk of MACE with the use of ustekinumab (OR 4.17; CI 1.19–14.59) [138]. A meta-analysis by Tzellos et al. of nine RCTs (five ustekinumab and four briakinumab) compared the risk of MACE in patients with psoriasis receiving IL-12/23 inhibitors versus those receiving placebo using the Peto one-step method, and found a statistically significant increased OR of 4.23 (CI 1.07–16.75) [139]. However, in another meta-analysis by Ryan et al. of the same data using a different method (Mantel–Haenszel fixed-effects method), there was no significant statistical difference in the rate of MACEs observed in patients with psoriasis receiving IL-12/23 inhibitors compared with placebo [140]. Of note, a large 5-year post-marketing study for psoriasis indicated that ustekinumab treatment does not increase the risk of MACE [141]. Similarly, several long-term studies support the safety of ustekinumab with regard to MACE risk [142, 143]. Further investigations are needed to confirm whether ustekinumab may have beneficial or detrimental effects on cardiovascular comorbidities in patients with psoriasis. Overall, we consider ustekinumab to be a third-line option.

5.3 IL-17 Inhibitors

Interleukin-17 may exert both pro-atherogenic and anti-atherogenic roles according to the specific context and microenvironment [144]. Despite these contradictory findings, the current clinical data at least indicate that IL-17 inhibitors did not increase the risk of cardiovascular disease [144]. In a pooled analysis of ten RCTs reviewing the safety data of secukinumab in 3993 patients with psoriasis, the exposure-adjusted incidence of MACE over 52 weeks was comparable across secukinumab 300 mg, secukinumab 150 mg, and etanercept (0.42, 0.35, and 0.34, respectively) [111]. Secukinumab treatment has been shown to improve the endothelial function of patients with psoriasis at 52 weeks assessed by flow-mediated dilation [145]. With regard to ixekizumab, data reported a low incidence of MACE with continued exposure for ixekizumab through 60 weeks, and the rates of MACE were similar between ixekizumab and etanercept [146]. Based on the data from phase III RCTs (UNCOVER-1, UNCOVER-2, and UNCOVER-3), ixekizumab exhibited a neutral impact on cardiovascular-related parameters in patients with psoriasis at week 60 [147]. As for brodalumab, a phase III RCT investigating the efficacy and safety of brodalumab in patients with psoriasis ($n = 661$) reported no cases of MACE during the 12-week induction phase and five cases of MACE over 52 weeks, suggesting a low rate of MACE for brodalumab [71]. Further investigations are required to confirm whether IL-17 inhibitors may have beneficial effects on the cardiovascular system in patients with psoriasis. Given the low risk of MACE associated with IL-17 inhibitors, we recommend these biologics as a second-line treatment.

5.4 IL-23 Inhibitors

From the present published RCT evidence, there is no safety signal for MACE with IL-23 inhibitors in patients with psoriasis [137]. Crowley et al. reviewed the safety data of IL-23 inhibitors (tildrakizumab, guselkumab, and risankizumab) from phase III RCTs in patients with psoriasis and reported no significant increase in MACE rates [148]. In a pooled analysis of three RCTs assessing the incidence of cardiovascular events among tildrakizumab-treated patients with psoriasis, there were no statistically significant difference in the risk of MACE with initiation of tildrakizumab as compared with placebo [149]. For guselkumab, a 5-year pooled analysis of two phase III RCTs (VOYAGE 1 and VOYAGE 2) showed a low incidence of MACE for guselkumab (0.29/100 patient-years) [150]. A recent analysis of adverse event reports in the FDA Adverse Event Reporting System revealed a potential safety signal for a cerebrovascular accident with the use of risankizumab in comparison to other alternative psoriasis therapeutics [151]. In order to better characterize this unconfirmed potential safety signal, further long-term observational data are necessary. Thus, we consider IL-23 inhibitors as a second-line treatment for patients with psoriasis and cardiovascular disease.

5.5 Small-Molecule Inhibitors

In a cohort study of 68,678 patients with PsA treated with apremilast, TNF-α inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and conventional treatments, the incidence rates of MACE were lowest for users of TNF-α inhibitors, and similar for all other treatments, including apremilast [152]. In another nationwide cohort study assessing the risk of MACE for patients with PsA, there were no statistically difference between apremilast new users and TNF inhibitors new users [136]. A 156-week long-term safety study of apremilast for patients with psoriasis reported a low incidence of MACE (0.5/100 patient-years) [153]. Therefore, we also recommend apremilast as a second-line treatment.

6 CHF

A nationwide cohort study has reported a psoriasis severity-dependent increased risk of congestive heart failure (CHF). The HRs for CHF in mild and severe psoriasis were 1.22 (95% CI 1.16–1.29) and 1.53 (95% CI 1.34–1.74) respectively, although the precise mechanism of this correlation is unclear [154].

6.1 TNF-α Inhibitors

The benefits of anti-TNF-α in patients with CHF is controversial. One RCT assessed the treatment safety and outcomes of infliximab in patients with the New York Heart Association class III and IV and a left ventricular ejection fraction less than 35%. Patients receiving high doses of infliximab (10 mg/kg) had an increased risk of hospitalization or death for CHF as compared with placebo (HR 2.84, CI 1.01–7.97) through 28 weeks [155]. Similar findings were supported in several case reports, with patients with psoriasis treated with TNF-α inhibitors experiencing a new onset or exacerbation of CHF. Lazarewicz et al. published a case of CHF that developed in a patient with rheumatoid arthritis receiving certolizumab pegol therapy, and the heart failure almost fully resolved after stopping the medication [156]. Furthermore, a case of sudden death after receiving a single infusion of infliximab 200 mg in a patient without CHF was reported [157]. Another case report described a patient with CD who developed CHF after infliximab treatment [158]. Recently, a case report presents a patient with relapsing hidradenitis suppurativa who was diagnosed with decompensated CHF after receiving adalimumab during hospitalization [159].

In contrast, some clinical data have suggested that etanercept treatment is beneficial for patients with CHF. An RCT ($n = 47$) of etanercept for patients with heart failure demonstrated a significant improvement in left ventricular ejection fraction and left ventricular remodeling in a dose-dependent manner [160]. Patients receiving etanercept 4 or 10 mg/m^2 experienced significant functional status improvements in another phase I study [161]. Although controversial, TNF inhibitors should be avoided in patients with CHF with New York Heart Association class III and IV, as well as patients with a left ventricular ejection fraction less than 50% [162]. Furthermore, echocardiogram and cardiology consultations are recommended before TNF inhibitor treatment in patients with CHF with the New York Heart Association class I or II [8].

6.2 IL-12/23 Inhibitors, IL-17 Inhibitors, and IL-23 Inhibitors

Clinical data on ustekinumab, anti-IL-17 agents, and anti-IL-23 agents are limited. A meta-analysis assessing the short-term risk of CHF in patients with psoriasis receiving ustekinumab, anti-IL-17 agents, and anti-IL-23 agents did not demonstrate any significant change in CHF incidence [163]. Han et al. compared the risk of CHF in patients with psoriasis receiving ustekinumab and TNF-α inhibitors. Patients initiated on ustekinumab exhibited a decreased risk of CHF compared with TNF-α inhibitors (HR 0.641; CI 0.415–0.985, $p = 0.0426$) [164]. In a phase III RCT ($n = 1346$) for patients with psoriasis, ixekizumab treatment reported no case of CHF [165]. A real-world study of secukinumab in patients with psoriasis with a 6-month follow-up reported no new onset or exacerbation of CHF [166]. Similarly, no CHF exacerbation or new onset was reported with brodalumab in a phase II open-label study with 5 years of long-term follow-up [167]. Preliminary clinical data have suggested that IL-12/23 inhibitors, IL-17 inhibitors, or IL-23 inhibitors appear to be safe for patients with CHF and concomitant psoriasis.

7 Depression

Many patients with psoriasis develop erythematous and scaly plaques on the visible areas of the body, resulting in a sense of stigma, lowered self-confidence, psychosocial burden, and depression [168]. The incidence of depression among patients with psoriasis is estimated to range from 32 to 60%, higher than that in the general population and other dermatology patients [169]. Although the psychological burden of psoriasis may be the source of depression, the strong association between psoriasis and depression is possible because of the overlapping inflammatory cytokines and shared physiological mechanisms [170].

7.1 TNF-α Inhibitors

A phase III RCT evaluated the effect of etanercept on the symptoms of depression in patients with psoriasis, as verified using the Beck Depression Inventory and Hamilton Rating Scale for Depression [171]. As a result, patients taking etanercept for 12 weeks had a meaningful improvement in Hamilton Rating Scale for Depression and Beck Depression Inventory scores compared with those receiving the placebo. Similarly, etanercept treatment significantly decreased both the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) score and the HADS-Depression (HADS-D) score in patients with psoriasis in a prospective cohort study [172]. However, sustained depression (HADS-D $\geq$ 8 at month 0 and month 1) was found to be associated with decreased PASI 75/90 responses to etanercept at month 6 [172]. Jin et al. also reported that patients with psoriasis with concomitant depression at baseline exhibited lower PASI 75/90 responses after 6 months of etanercept treatment compared with control patients [173]. According to the real-world study data, adalimumab therapy was associated with a decreased risk of depression compared with conventional systemic agents (HR 0.63, CI 0.46–0.86) [174]. Furthermore, adalimumab treatment led to a significant improvement in depressive symptoms in patients with psoriasis [175].

7.2 IL-12/23 Inhibitors

In a phase III RCT (n = 1230), patients with psoriasis receiving ustekinumab experienced a large improvement in HADS and Dermatology Life Quality Index scores [176]. Ustekinumab was tested in an open-label trial and also has been shown to significantly relieve the depressive symptoms in patients with psoriasis, as assessed by Beck Depression Inventory scores and psychiatric interviews [177].

7.3 IL-17 Inhibitors

In a pooled analysis of three phase III RCTs for patients with psoriasis affected by moderately severe depressive symptoms (Quick Inventory of Depressive Symptomatology-Self-Report 16 score $\geq$ 11), about 40% of comorbid patients initiated on ixekizumab exhibited depression remission (Quick Inventory of Depressive Symptomatology-Self-Report 16 score $\leq$ 5), while only 17.8% of patients receiving placebo showed depression remission [178]. A post hoc analysis of a phase IIIb RCT (SUPREME; n = 434) reported that secukinumab treatment led to improvement in symptoms of anxiety/depression for 48 weeks, as verified using HADS [179]. Furthermore, 80–87% of patients with psoriasis treated with secukinumab experienced a PASI 90 response, regardless of baseline depression/anxiety status. Strober et al. performed a pooled analysis of ten clinical trials in patients with psoriasis and reported that secukinumab treatment did not increase the risk of depression, anxiety, or suicidality [180]. However, Komori et al. presented a case of depression exacerbation in a patient with PsA initiated on secukinumab [181]. The safety of brodalumab on depression remains controversial because of the enhanced number of suicidal ideation and behavior cases observed in the patients treated with brodalumab [181]. However, Chiricozzi et al. demonstrated that there is an accidental but not causal association between suicidal behavior events and brodalumab use [182]. Furthermore, brodalumab treatment resulted in an improvement in depression/anxiety scores versus placebo [182].

7.4 IL-23 Inhibitors

In a phase IIII RCT (VOYAGE2; n = 992), more patients with psoriasis with baseline Hospital Anxiety and Depression Scale-Anxiety or HADS-D $\geq$8 reported Hospital Anxiety and Depression Scale-Anxiety or HADS-D <8 after receiving guselkumab for 24 weeks compared with adalimumab (anxiety: 58.4% vs 42.9%, p = 0.028; depression: 59.8% vs 46.4%, p = 0.079) [183]. Reich et al. also analyzed the data from VOYAGE2 and reported that guselkumab therapy was associated with greater improvements in work productivity compared with adalimumab in patients with psoriasis with or without depression/anxiety status [184]. Augustin et al. combined data from UltIMMa-1 and 2 of risankizumab (n = 997) and demonstrated that risankizumab treatment had a superior effect in reducing psychological distress compared with ustekinumab (anxiety: 69.1% vs 57.1%, p = 0.004; depression: 71.1% vs 60.4%, p = 0.01) [185].

Interleukin-23 inhibitors are the first-line choice as they seem to be more effective in improving symptoms of anxiety and depression than TNF inhibitors and ustekinumab. Because brodalumab may increase the risk of suicide ideation cases, we recommended carefully assessing the use of brodalumab in patients with psoriasis with a history of psychiatric comorbidities. Other IL-17 inhibitors and ustekinumab are the second-line options as several clinical trials have shown good tolerance and efficacy for depression. While depression symptoms in patients with psoriasis decreased the treatment response to TNF inhibitors, this class should be considered a third-line treatment for patients with psoriasis with depression.

8 MS

Psoriasis and MS are both T-cell-mediated autoimmune diseases. In a meta-analysis of nine observational studies, psoriasis has been associated with an increased risk of developing MS (RR 1.607; CI 1.322–1.953, p < 0.0001) [186].

According to data from a national cohort study in Denmark, the association between psoriasis and MS became stronger as psoriasis became more severe (adjusted incidence rate ratios 1.84, and 2.61 for mild and severe psoriasis, respectively) [187]. Although the mechanism is unclear, accumulating evidence suggests that pathophysiological factors may be responsible for the relationship between psoriasis and MS. Both diseases have an aberrant immune infiltration of Th17 cells with the production of IL-17 [187]. Additionally, the two diseases share genetic links such as polymorphisms within the IL-23 receptor gene [188].

8.1 TNF-α Inhibitors

Although TNF-α inhibitors have been commonly used in immune-mediated disorders, they were ineffective in patients with MS and even exacerbated MS. A phase II RCT ($n = 168$) evaluated the effects of lenercept, a TNF receptor fusion protein-like etanercept (did not progress to market), on the number of new lesions in MS up to 48 weeks. As a result, obviously greater proportions of patients treated with lenercept experienced MS exacerbations compared with placebo-treated patients [189]. In a phase I safety trial of infliximab, leukocyte counts and immunoglobulin in cerebrospinal fluid significantly increased in two patients with rapidly progressive MS after treatment with infliximab, suggesting TNF neutralization increased the disease activity of MC and caused immune activation [190]. Several case reports supported similar results, with TNF-α inhibitor treatment worsening the signs and symptoms of MS. Sukal et al. described a patient with psoriasis treated with etanercept who developed neuroradiological and clinical signs of MS after 1 year of the therapy [191]. Another patient with psoriasis who received infliximab developed MS during treatment, and the neurological symptoms resolved after discontinuation of infliximab [192]. Furthermore, another case report presented a patient with PsA and uveitis who manifested MS after treatment with adalimumab [193]. Therefore, it is best to avoid this class of drugs in patients with psoriaswith established demyelinating disease.

8.2 IL-17 Inhibitors

Secukinumab was tested in a phase II RCT for patients with MS and has been shown to dramatically reduce the number of new active brain lesions in patients with MS compared with placebo [194]. A case report described a patient with PsA with concomitant MS status who responded unsatisfactory to ustekinumab, secukinumab treatment reduced the psoriasis activity and halted the MS deterioration [195]. In the cuprizone-induced MS experimental model, secukinumab treatment played a neuroprotective effect by modulating oxidative and inflammatory signaling [196]. In a case study of the co-occurrence of psoriasis and MS, treatment with ixekizumab resulted in complete skin clearance without MS progression [197]. Based on the evidence provided by clinical trials and case reports, the use of anti-IL-17 agents could be a safe and promising option for patients with psoriasis with concomitant MS.

8.3 IL-12/23 Inhibitors

Chang et al. presented two patients with psoriasis with comorbid MS who were treated with ustekinumab and achieved clinical remission without MS progression after treatment [198]. However, patients receiving ustekinumab did not demonstrate superior efficacy in reducing the MS lesions compared with placebo in another phase II clinical trial, though ustekinumab was well tolerated for patients with MS [199]. Thus, in patients with psoriasis and MS, ustekinumab is a second-line treatment option.

8.4 IL-23 Inhibitors

Data on anti-IL-23 agents are limited, but there are no reports that these drugs lead to disease worsening of MS. Based on the data from three phase III RCTs ($n = 2081$), Blauvelt et al. assessed the long-term safety of tildrakizumab in psoriasis and reported no cases of MS after 64 weeks of therapy [200]. A phase III RCT exploring the safety of guselkumab versus placebo and adalimumab in psoriasis did not report any MS cases or MS exacerbations [201]. Similarly, there was no adverse event of MS during risankizumab treatment in a phase III RCT [202]. Given the limited evidence, anti-IL-23 agents are considered a third-line treatment option.

9 Malignancy

Increasing evidence suggests that patients with psoriasis might have a higher risk of malignancy, especially non-melanoma skin cancer (NMSC) and lymphoma, compared with psoriasis-free patients [203, 204]. A cohort study conducted by Margolis et al. revealed that patients with psoriasis had a higher risk of overall malignancy (RR 1.78; CI 1.30–2.40) [205]. Although the reasons for this increased risk are still inconclusive, it seems evident that chronic inflammation conditions and immunosuppressive therapies play important roles in the pathogenesis of tumors [206].

9.1 TNF-α Inhibitors

Considering the role of TNF in mediating tumor growth, concerns remain about the risk of malignancy with anti-TNF therapy. In a meta-analysis assessing the short-term risk of

NMSC in patients receiving anti-TNF inhibitors (including RA, psoriasis, PsA, ankylosing spondylitis, and CD), the relative risks associated with anti-TNF inhibitors were 2.02 (95% CI 1.11–3.95) [207]. Another study supported the similar findings, with patients with psoriasis receiving TNF inhibitors showing an increased incidence of NMSC, especially cutaneous squamous cell carcinoma (adjusted HR 1.81; CI 1.23–2.67) [208]. An increase of developing all cancers has been found in patients with psoriasis treated with adalimumab and infliximab compared with the general population in a pooled analysis of 71 controlled trials (OR 3.3; CI 1.2–9.1) [209]. The association between tumorigenesis and anti-TNF therapy was also documented in multiple case reports [210–212]. In contrast, based on the data of two meta-analyses and one observational study, TNF inhibitors did not meet the statistical significance in increasing the risk of malignancy [213–215]. Overall, it is best to avoid this class of drugs in patients with psoriasis with concomitant malignancy.

9.2 IL-17 Inhibitors

Gottlieb et al. summarized the incidence of malignancy in patients with psoriasis with brodalumab treatment (n = 4019) based on the data of one phase II study and three phase III RCTs, reporting two cases of lymphomas and three cases of NMSC. In particular, significantly lower rates of malignancy at 52 weeks were identified in patients receiving brodalumab, as compared with ustekinumab-treated patients [216]. In a integrative analysis of ten clinical trials (n = 3430), three NMSC cases were reported in patients with psoriasis during secukinumab treatment, suggesting that secukinumab did not lead to an increased risk in malignancy [111]. Likewise, the safety data from seven clinical trials of ixekizumab in patients with psoriasis (n = 4209) demonstrate a low incidence of malignancy with long-term exposure to ixekizumab [146].

9.3 IL-23 Inhibitors

Two RCTs assessing the safety of guselkumab in psoriasis (n = 825) reported three cases of NMSC and no lymphoma cases. In a pooled analysis of two RCTs, Reich et al. evaluated the long-term treatment outcomes and safety of tildrakizumab in psoriasis for up to 148 weeks and reported low exposure-adjusted rates of malignancies [217]. Based on the safety data from two phase III RCTs (n = 997), NMSC was reported in two patients with psoriasis after 18 weeks of exposure to risankizumab [202]. As anti-IL-17 and anti-IL-23 therapies have low rates of malignancy, they are considered first-line options in patients with psoriasis with malignancy.

9.4 IL-12/23 Inhibitors

Papp et al. assessed the long-term safety of ustekinumab in patients with psoriasis (n = 3117) for up to 5 years and reported 47 cases of NMSC and 54 cases of other malignancies, the rates of which were comparable with rates expected in the general population [218]. The impact of ustekinumab treatment on malignancy risk was also evaluated in another study and did not demonstrate an obvious increase in the risk of malignancies compared with no exposure [219]. Similarly, the safety data from pooled phase II and III RCTs of ustekinumab in patients with psoriasis (n = 3117) did not suggest higher rates of malignancy with ustekinumab exposure [220]. However, in animal studies, prolonged treatment with ustekinumab was associated with an increased risk of tumor development [221]. Overall, ustekinumab may be considered a second-line agent.

10 Conclusions

The development of multiple powerful biologic agents and small-molecule inhibitors has broadened the treatment regimens and transformed patient outcomes for psoriasis. However, comorbid disease conditions often complicate the clinical therapy decision, and it is important to consider the strengths and limitations of each biologic agent when formulating a personalized treatment protocol for patients with psoriasis. We hope our evidence-based recommendations can help guide dermatologists in selecting appropriate biologic therapy for individuals with comorbid PsA, obesity, depression, IBD, CHF, MS, and malignancy. Accordingly, the therapeutic guidelines should be modified as more strong evidence emerges.

Declarations

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