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CURRENT OPINION

Biologic Treatment Algorithms for Moderate-to-Severe Psoriasis with Comorbid Conditions and Special Populations: A Review

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Abstract

The emergence of data from clinical trials of biologics, the approval of new biologics, and our improved understanding of psoriasis pathogenesis have increased the therapeutic possibilities for the treatment of moderate-to-severe psoriasis. Biologics currently approved for the treatment of psoriasis include tumor necrosis factor inhibitors, interleukin (IL)-17 inhibitors, ustekinumab (an IL-12/23 inhibitor), and IL-23 inhibitors. Data from clinical trials and studies of the safety and efficacy of biologics provide essential information for the personalization of patient care. We discuss the benefits and disadvantages of biologics as a first-line treatment choice, update treatment recommendations according to current evidence, and propose psoriasis treatment algorithms. Our discussion includes the following comorbid conditions: psoriatic arthritis, multiple sclerosis, congestive heart failure, inflammatory bowel disease, hepatitis B, nonmelanoma skin cancer, lymphoma, and latent tuberculosis. We make evidence-based treatment recommendations for special populations, including pediatric patients, patients with coronavirus 2019 (COVID-19), and pregnant and breastfeeding patients with psoriasis. Ultimately, individualized recommendations that consider patient preferences, disease severity, comorbid conditions, and additional risk factors should be offered to patients and updated as new trial data emerges.

1 Introduction

Psoriasis is a chronic condition with several systemic and immune manifestations that affects more than 125 million people worldwide [1–3]. Studies have shown associations between psoriasis and other conditions, including psoriatic arthritis (PsA), multiple sclerosis (MS), congestive heart failure (CHF), inflammatory bowel disease (IBD), malignancy, and mood disorders [2, 4, 5]. Several effective psoriasis treatments have emerged within the last decade [6]. Approved biologics for the treatment of moderate-to-severe

Key Points

Psoriasis and comorbid conditions require specialized treatment protocols with respect to the safety and efficacy of biologics to achieve treatment goals.

Clinical trials have led to newly approved biologics for the treatment of moderate-to-severe psoriasis, providing unique treatment options for patients with psoriasis and comorbid conditions; initial biologic treatment choice varies with disease severity, clinical presentation, and patient preferences.

We provide evidence-based recommendations for consideration in patients with concurrent psoriasis and active coronavirus disease 2019 (COVID-19) infection.

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psoriasis include tumor necrosis factor inhibitors (TNFi: infliximab, etanercept, adalimumab, certolizumab pegol), interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, brodalumab), an IL-12/23 inhibitor (ustekinumab), and IL-23p19 inhibitors (guselkumab, tildrakizumab, risankizumab) [4, 5]. Moreover, several biologics (e.g., bimekizumab and mirikizumab) and small-molecule therapies (deucravacitinib) are in development, complicating treatment decisions. We aim to provide an update of the evidence-based treatment recommendations for individuals with psoriasis.

2 Approach to the Evidence

Our review objective was to create evidence-based treatment algorithms derived from existing literature. We provide biologic treatment algorithms for moderate-to-severe psoriasis in patients with comorbidities and in special populations. Treatment algorithms are organized as follows:

- Medications within a biologic class and with similar efficacy and safety profiles are separated by commas.
- If all of the drugs of a class are assigned equal weight, the class is listed (e.g., IL-17 inhibitors) in place of individual biologic agents.

3 Comorbid Conditions and Special Populations

Important considerations:

- Our recommendations are not definite. Physicians should create an optimal treatment plan with respect to patient-related factors and comorbid conditions.
- For clinical scenarios lacking high-quality evidence from large-scale randomized controlled trials (RCTs), lower-quality studies, including case reports, proof-of-concept studies, and studies with small sample sizes are utilized.
- Barriers to patient care, such as transport and insurance, are not taken into consideration.

3.1 Patients with Psoriasis and Psoriatic Arthritis

PsA affects 20–30% of patients with psoriasis [1, 7–9]. Since psoriasis can occur concurrently with or as a predecessor to PsA, early detection and referral to rheumatologists is essential to preserve joint function and prevent debilitating joint damage [1, 10].

A phase IIIB/IV RCT compared ixekizumab ($n = 283$) and adalimumab ($n = 283$) in patients with PsA and active psoriasis ($\geq 3\%$ of body surface area) for 24 weeks [11]. Ixekizumab maintained superior efficacy compared with adalimumab for 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI100) (ixekizumab 60.1%, adalimumab 46.6%; $p = 0.001$) and 50% improvement from baseline in American College of Rheumatology criteria (ACR50) (ixekizumab 50.5%, adalimumab 47%; $p = 0.338$) with fewer severe adverse events (AEs) (ixekizumab 3.5%, adalimumab 8.5%) [11]. Through 52 weeks, 64.3% of patients receiving ixekizumab and 41.3% of those receiving adalimumab achieved PASI100 ($p < 0.001$); responses in terms of ACR50 were similar for both drugs (49.8 vs. 49.8%; $p = 0.924$) [12]. Ixekizumab showed improvement in quality-of-life measures and a moderate safety profile in PsA with comorbid psoriasis in two phase III RCTs [13, 14]. Another phase III RCT ($n = 996$) evaluated secukinumab 150 mg/300 mg, with or without a loading dose (LD), compared with placebo in patients with PsA and concomitant psoriasis [15]. Patients receiving secukinumab 300 mg with LD ($p < 0.01$), 150 mg without LD ($p < 0.01$), and 150 mg with LD ($p < 0.05$) experienced significant clinical improvement in PsA, and radiologic progression was inhibited by week 24, with AE rates (approximately 62%) comparable across all four treatment arms [15]. The low rate of radiologic progression was maintained through week 156 in patients with and without psoriasis [16–18]. In a phase IIIb RCT ($n = 853$) in patients with PsA and comorbid psoriasis evaluating secukinumab compared with adalimumab, secukinumab did not show significant superiority over adalimumab (PASI90, $p < 0.001$; ARC50 $p < 0.2251$) [19].

In two phase III RCTs (PSUMMIT 1 AND 2; $n = 546$ psoriasis and PsA/747 total PsA), ustekinumab resulted in decreased radiologic progression compared with placebo [20]. Additionally, more patients receiving ustekinumab 45 or 90 mg experienced complete resolution of enthesitis and dactylitis by week 24 compared with placebo [20]. Analysis of the BIOPURE (Biologic Apulian) registry ($n = 160$) showed longer 12-month drug survival of ustekinumab and better clinical outcomes in TNFi-naïve patients with PsA [21].

In the phase III DISCOVER-1 RCT ($n = 362$) and phase II RCT ($n = 149$), guselkumab led to significant improvements in physical function and psoriasis [22, 23]. Additionally, guselkumab maintained a stable safety profile in phase III RCTs [24, 25].

The follow-up time is longer for TNFi than for IL-17 inhibitors and IL-12/23 inhibitors [10]. TNFi are among the first choices for PsA because the clinical evidence supporting efficacy and inhibition of radiologic progression is consistent [26, 27]. Guselkumab is the second-line treatment as it has proven efficacy and mild side effects [28]. Ustekinumab is the third-line treatment option as several studies have shown efficacy for PsA. Phase III trials are ongoing for IL-23 inhibitors (tildrakizumab) and IL-17 inhibitors (brodalumab) for approval in PsA [29, 30].

Expert opinion algorithm:

1. TNFi or IL-17 inhibitors
2. Guselkumab
3. Ustekinumab

3.2 Patients with Psoriasis and Multiple Sclerosis

Individuals with psoriasis may have increased risk for MS because of an overactive immune system [31, 32]. TNFi are not recommended for individuals with MS or with a first-degree relative with MS [31, 33–41].

IL-17 inhibitors have been shown to reduce MS lesion activity on radiographic studies [5, 31, 42]. In a phase II RCT ($n = 73$) to assess the effects of secukinumab on number of new active lesions in patients with MS, secukinumab significantly reduced the number of unique active MS lesions compared with placebo [42]. In a case study of concomitant psoriasis and MS, secukinumab reduced psoriasis activity, but the patient experienced severe MS relapse [43]. In three additional reports, secukinumab achieved clinical improvement in psoriasis without MS progression [44–46]. Therefore, we recommend IL-17 inhibitors as the first-line treatment [32].

In a phase II RCT ($n = 249$) evaluating ustekinumab for the treatment of patients with MS, ustekinumab was well-tolerated but failed to show efficacy in slowing MS progression [47]. A phase III RCT (PHOENIX-1; $n = 766$), pooled phase II RCTs, and recent case reports ($n = 2$) have all demonstrated ustekinumab to be efficacious for psoriasis without reports of MS or progression of lesions [48–51]. Thus, ustekinumab should be a second-line treatment for patients with psoriasis and MS.

Pooled analysis of three RCTs ($n = 2081$) evaluating the safety of tildrakizumab in psoriasis reported no MS AEs [52]. Two phase III RCTs ($n = 997$) evaluating the safety of risankizumab compared with ustekinumab or placebo did not report any MS cases/exacerbations in patients with psoriasis [53]. Similarly, no cases of MS exacerbation were reported in multiple RCTs with guselkumab [54–56]. The available data for psoriasis with comorbid MS are limited, possibly because patients with MS were excluded from phase III RCTs.

Expert opinion algorithm:

1. IL-17 inhibitors
2. Ustekinumab
3. IL-23 inhibitors
4. Avoid TNFi in patients with MS

3.3 Patients with Psoriasis and Congestive Heart Failure

Patients with psoriasis have an increased risk of cardiovascular diseases and new-onset CHF [57, 58]. Currently, TNFi are not recommended in patients with New York Heart Association (NYHA) class III and IV CHF [59–62]. Several case reports have shown new-onset or exacerbation of CHF in patients treated with TNFi [61, 63]. An RCT ($n = 150$) studying infliximab in NYHA class III or IV CHF indicated that infliximab 10 mg resulted in an increased risk of mortality and hospitalizations compared with placebo (hazard ratio [HR] 2.84; 95% confidence interval [CI] 1.01–7.97; $p = 0.043$) [62, 64]. Data from case reports supported similar findings, with patients receiving TNFi experiencing new-onset CHF or exacerbation of symptoms [63]. Before initiation of TNFi in NYHA class I and II CHF, the patient should undergo a cardiology consultation, and clinicians should obtain a baseline echocardiogram to assess ejection fraction [59, 65, 66]. TNFi should be avoided in patients with reduced ejection fraction < 50% [66]. If CHF worsens or new symptoms develop, TNFi should be discontinued [5, 65, 66].

A 5-year phase II RCT of brodalumab ($n = 181$) reported no cases of CHF [67]. Moreover, no CHF exacerbations or new-onset CHF were reported in a 6-month follow-up of patients in the secukinumab registry [68], and no cases of CHF were reported with ixekizumab in three phase III RCTs ($n = 3736$) [69, 70].

Two RCTs of ustekinumab, PHOENIX 1 ($n = 601$) and 2 ($n = 849$), reported no cases of CHF [71, 72].

In a meta-analysis of RCTs, patients initiated on IL-23 or IL-17 inhibitors did not exhibit an increased risk of CHF (risk difference 0.00; 95% CI -0.01–0.01) [73]; however, the data presented in this study should be evaluated carefully as only the short-term risk of CHF was considered [73].

Expert opinion algorithm:

1. IL-17 inhibitors, IL-23 inhibitors, ustekinumab
2. Avoid TNFi
   - Avoid in NYHA class III and IV
   - Echocardiogram is recommended in NYHA class I and II
   - Avoid in patients with ejection fraction <50%

3.4 Patients with Psoriasis and Inflammatory Bowel Disease

Psoriasis is associated with both Crohn's disease (CD) and ulcerative colitis (UC) [74]. Therapies used for the treatment of psoriasis can potentially exacerbate or induce IBD [74].

Likewise, medications used for the treatment of IBD have been noted to worsen psoriasiform lesions [75].

Adalimumab, infliximab, and certolizumab were significantly associated with the induction and maintenance of remission for CD compared with placebo in a meta-analysis of 19 controlled trials [76]. Adalimumab and infliximab are approved for the treatment of UC and CD, and certolizumab is approved for the treatment of CD [77]. Adalimumab and infliximab maintained similar treatment persistence levels in UC ($n = 160$) and CD ($n = 487$) in retrospective observational studies [78, 79]. In a phase III RCT in patients with CD, infliximab induced clinical remission ($n = 75$; $p = 0.02$) and mucosal healing ($n = 28$; $p = 0.06$) by week 26 [80]. In a pooled analysis of two RCTs ($n = 938$), adalimumab improved laboratory and quality-of-life markers in UC ($p < 0.05$ and $p < 0.001$) compared with placebo [81]. In a phase III RCT ($n = 521$), adalimumab successfully induced remission for UC compared with placebo [82]. The US FDA Adverse Event Reporting System (FAERS) includes 443 cases of new-onset IBD and 43 cases of IBD exacerbation associated with etanercept [83]. In eight patients, IBD symptoms resolved upon discontinuation of etanercept. Physicians should maintain vigilance for gastrointestinal symptoms [83]. In a nationwide study of autoimmune diseases, etanercept was associated with a significant risk of de novo CD (adjusted HR [aHR] 2.0; 95% CI 1.4–2.8) and de novo UC (aHR 2.0; 95% CI 1.5–2.8) [77].

A pooled analysis of 21 controlled trials of secukinumab showed a low incidence of IBD in psoriasis ($n = 5181$), with a total of 20 (14 new-onset) IBD cases [84]. In total, 15% of patients with psoriasis had prior exposure to biologic therapy with an inadequate response [84]. Pooled data from seven controlled trials of ixekizumab showed a low incidence of IBD in patients with psoriasis (19/4209) [85].

A phase II RCT of brodalumab in 130 patients with active CD was terminated early because of a disproportionate number of worsening CD cases and lack of efficacy [86]. Thus, brodalumab should be avoided in cases of active CD [86, 87].

Clinicians should prescribe IL-17 inhibitors with caution, as FDA information warns against using the class in IBD [88–90].

In the UNITI-1/2 RCTs ($n = 718$) in patients with CD, ustekinumab maintained clinical response and remission through week 92 without new safety signals [91]. An endoscopic substudy of RCTs ($n = 334$) showed endoscopic improvement after 8 weeks of ustekinumab treatment ($p = 0.012$) compared with placebo [92]. However, a cohort study ($n = 163$) comparing adalimumab and ustekinumab reported that adalimumab produced better clinical response (aOR 2.40; 95% CI 1.14–5.07) and remission rates (aOR 2.35; 95% CI 1.07–5.16) [93]. Ustekinumab was approved for UC by the FDA in 2019 after a phase III RCT demonstrated effective remission induction and mucosal healing [94].

Currently, trials are investigating IL-23 inhibitors for the treatment of psoriasis with IBD. One RCT comparing risankizumab and secukinumab reported no IBD cases for risankizumab ($n = 164$) and one UC case in patients receiving secukinumab ($n = 163$) [95]. Other studies comparing risankizumab versus ustekinumab, risankizumab versus adalimumab, and guselkumab versus secukinumab also reported no IBD cases [53, 96, 97].

Overall, adalimumab and infliximab should be considered first-line agents for patients with IBD and psoriasis. Ustekinumab and certolizumab have demonstrated efficacy in CD, and ustekinumab was recently approved for UC. IL-23 inhibitors are newly developed biologic agents with good efficacy and safety profiles. Patients should be monitored for symptoms of IBD for up to 4 years after initiation of IL-17 inhibitors [98]. Similarly, etanercept has been reported to induce exacerbation of IBD.

Expert opinion algorithm:

1. Adalimumab, infliximab (approved for CD and UC)
2. Certolizumab (approved for CD), ustekinumab (approved for CD and UC)
3. IL-23 inhibitors
4. Etanercept
5. Avoid IL-17 inhibitors in patients with IBD

3.5 Patients with Psoriasis and Hepatitis B

Over 250 million people worldwide are infected with hepatitis B virus (HBV), with chronic infection resulting in severe complications [99, 100]. As biologics are immunosuppressive agents, concern remains for reactivation of HBV. To ensure appropriate treatment recommendations, HBV screening with triple serology (including hepatitis surface antigen [HBsAg], antibodies to hepatitis core antigen [anti-HBc], and antibodies to hepatitis surface antigen [anti-HBs]) and liver function tests (LFTs) are recommended before initiation of biologics [101].

TNFi are associated with a risk of HBV reactivation and drug-induced liver injury, especially in HBsAg-positive patients with psoriasis [102, 103]. Seropositivity for HBsAg has a higher risk without antiviral prophylaxis (12–39%) than with antiviral prophylaxis (1–10%). The risk is lower with seropositivity anti-HBc [102, 103]. A multicenter study of patients with psoriasis with hepatitis B ($n = 359$) or hepatitis C ($n = 61$) treated with two or more immunosuppressants (including biologics) ($p = 0.0223$) reported the following predictive factors for viral reactivation: HBsAg-seropositivity ($p < 0.0001$), hepatitis B e-antigen positivity ($p = 0.0134$), and absence of antiviral prophylaxis ($p = 0.046$) [104]. The study also supported a lower risk of

reactivation with antiviral prophylaxis and recommended viral load monitoring. The risk of reactivation was higher with TNFi than with IL-17 inhibitors (aHR 2.67; 95% CI 1.08–6.58) [104]. A retrospective cohort study ($n = 30$) and systematic review (49 studies, $n = 312$) evaluated patients with hepatitis B or C with psoriasis receiving biologic therapy [105]. Yearly reactivation rates were higher in patients with chronic hepatitis B (13.92%) than with patients with resolved hepatitis B (0.32%) on TNFi therapy, and the risk was higher in patients who did not receive antiviral prophylaxis (26.31%) [105].

A 1-year brodalumab pharmacovigilance update ($n = 826$) reported no cases of hepatitis B; further data are needed to evaluate the safety profile [106]. Three phase III RCTs ($n = 3736$) demonstrated the clinical efficacy of ixekizumab for patients with psoriasis, with no reported cases of hepatitis B reactivation through week 60 [70]. In a prospective secukinumab cohort study with 49 patients with hepatitis B, HBsAg-positive patients had a higher risk of reactivation than HBs-Ag-negative and HBcAg-positive patients (24.0 vs. 4.17%; $p = 0.047$) [107]. However, reactivation rates were lower with antiviral prophylaxis (0%) than without (15.2%) for the same groups. Patients on secukinumab should receive antiviral prophylaxis to prevent viral reactivation and routine monitoring for HBV viral load [107].

In a prospective cohort study ($n = 93$) of ustekinumab in patients with psoriasis, inactive HBV carriers experienced a reactivation rate of 17.4% without antiviral prophylaxis compared with no cases with prophylaxis [108]. One patient with reactivation was concurrently treated with methotrexate [108]. Two additional retrospective cohort studies concluded ustekinumab was safe and efficacious to use in patients with psoriasis and hepatitis B with proper monitoring and antiviral prophylaxis [109, 110]. As studies of viral hepatitis and psoriasis are limited to small sample sizes, further data from RCTs are needed to evaluate the safety and efficacy of ustekinumab in psoriasis with concomitant hepatitis B.

No trials have specifically studied IL-23 inhibitors in patients with psoriasis and hepatitis [111–113]. However, a phase III RCT ($n = 739$) evaluating guselkumab in PsA reported one case of hepatitis B [25]. Another phase III RCT of guselkumab ($n = 381$) in patients with PsA reported no cases of hepatitis B [22]. Analyses of phase III RCTs with tildrakizumab and risankizumab also reported no cases of hepatitis [53, 114]. As IL-23 inhibitors are a novel class of drugs with no to minimal reported cases of hepatitis B in RCTs, we recommend this class as a second-line treatment.

Overall, before immunosuppressive therapy is initiated, especially TNFi, we recommend consultation with a hepatologist and triple serology screening with LFTs in all patients with psoriasis with a history of hepatitis B [5, 102, 105, 115, 116]. Serologic risk stratification between nonimmune, immune due to vaccination, resolved previous hepatitis infection, acute infection, chronic infection, and occult infection will allow appropriate initiation of antiviral prophylaxis and/or vaccination. Further, antiviral prophylaxis and testing for HBV reactivation should be continued for 6–12 months after biologic therapy cessation [117].

Expert opinion algorithm:

1. IL-17 inhibitors
2. IL-23 inhibitors
3. Ustekinumab or TNFi

3.6 Patients with Psoriasis and Latent Tuberculosis

Screening for latent tuberculosis infection (LTBI) and a full clinical history/physical examination are recommended for patients with psoriasis prior to initiation of biologics [118, 119]. Patients should be asked about recent exposure to tuberculosis, treatment history, and treatment course/compliance [118]. A tuberculin skin test or an interferon gamma assay are strongly recommended before initiation of biologic therapy [119]. If clinical suspicion is high, patients should receive a chest X-ray [119]. In LTBI diagnosis, prophylactic treatment with isoniazid 300 mg and vitamin B_6 50 mg for 9 months is advised [5, 119]. However, patients with LTBI can be started on biologics after 1–2 months of LTBI prophylaxis and demonstrated treatment compliance/tolerance if needed [119].

The use of TNFi in rheumatologic and dermatology conditions, including PsA, has been associated with serious tuberculosis infection [65, 120–122]. The World Health Organization issued a black box warning for the risk of tuberculosis and other serious infections with TNFi [123]. Further, a review indicated patients with LTBI treated with TNFi have an approximately two to four times increased risk of developing active tuberculosis [124]. A pooled analysis of controlled trials for numerous conditions yielded one case of tuberculosis in patients on certolizumab [125]. A meta-analysis of 29 RCTs reported that 45/7912 (0.57%) patients developed tuberculosis after treatment with TNFi [126]. Over a 7-year period, six cases of active tuberculosis were reported in adult patients with psoriasis on adalimumab in the ESPIRIT registry ($n = 6051$) [127]. A study analyzing adalimumab safety data from 18 controlled trials reported 16 cases of tuberculosis (seven LTBI, nine active tuberculosis) in 3723 patients with psoriasis [128]. A similar study that analyzed 77 controlled trials of adalimumab for various conditions reported a tuberculosis incidence rate (IR) of 0.2 in patients with psoriasis ($n = 3732$) [129]. Analysis of infliximab treatment for dermatologic and rheumatologic conditions revealed 70 cases of active tuberculosis after treatment initiation in FAERS [130].

The following cases of tuberculosis reactivation have been reported: 0/826 in a 1-year pharmacovigilance study

of brodalumab, 0/5898 in cumulative data from 13 clinical trials of ixekizumab, 0/2044 in an analysis of pooled safety data from five RCTs of secukinumab, 0/3430 in an analysis of pooled safety data in ten RCTs of secukinumab, and one patient without prophylaxis/3117 in an analysis of pooled safety data from four RCTs of ustekinumab [49, 106, 131–133]. Furthermore, five pooled phase III RCTs of ustekinumab ($n = 3177$) reported no cases of LTBI reactivation with antituberculosis prophylaxis [134].

Two phase III RCTs of guselkumab reported no cases of LTBI reactivation or active tuberculosis compared with two cases of LTBI reactivation with adalimumab in patients with psoriasis [135]. Four phase III RCTs of risankizumab reported no cases of active tuberculosis [53, 95, 96]. Two phase III tildrakizumab RCTs reported no cases of tuberculosis [114].

Evaluation of LTBI before initiating biologic therapy, as well as follow-up and routine monitoring with antiviral prophylaxis, are indicated [5, 88–90, 111–113, 136–140]. As low rates of tuberculosis reactivation have been reported with IL-23 and IL-17 inhibitors, and their long-term safety profiles are favorable, they are first in our algorithm. Since TNFi increase the risk of serious tuberculosis infection, this class is a last-line option. At least 1 month of antiviral prophylaxis is recommended before initiating ustekinumab and TNFi therapy.

Expert opinion algorithm:

1. IL-17 inhibitors or IL-23 inhibitors
2. Ustekinumab or TNFi after tuberculosis prophylaxis

3.7 Pediatric Patients with Psoriasis

Psoriasis accounts for approximately 4% of pediatric dermatoses, with up to 33% of cases starting in childhood [141]. Pediatric patients with psoriasis are reported to have double the occurrence of comorbidities than their peers [141]. Pediatric patients have previously been managed according to data from adult controlled trials, but pediatric controlled trials are emerging to help guide management [142]. However, caution is still advised when prescribing biologics for psoriasis treatment [5].

Weekly etanercept is approved for the treatment of patients aged ≥ 4 years with moderate-to-severe psoriasis [141]. A retrospective cohort study examining patients aged ≤ 17 years ($n = 23$) receiving etanercept reported that 56.5% achieved PASI75 and 86.9% achieved PASI50 by week 12, with treatment efficacy maintained at week 52 [143]. PASI75 and PASI90 were maintained by approximately 65% and 35% of patients, respectively, through 5 years in an open-label extension study (69/181) [144]. AEs were reported by 161 (89.0%) of the patients and included upper respiratory tract infection (37.6%), nasopharyngitis (26.0%), and headache (21.55%), with seven patients experiencing eight severe AEs [144]. Limitations include the small number of patients completing the study through week 264 [144, 145]. With a high percentage of patients affected by AEs, etanercept is third in our algorithm.

The European Medicines Agency (EMA) approved adalimumab for the treatment of psoriasis in patients aged ≥ 4 years. A retrospective observational study involving 134 patients compared etanercept ($n = 63$), adalimumab ($n = 44$), and ustekinumab ($n = 27$) [146]. The drug survival rate was highest for ustekinumab compared with etanercept and adalimumab ($p < 0.0001$). Severe AEs of infections and weight gain were reported with adalimumab (six) and etanercept (one) [146]. A phase III RCT treated 114 pediatric patients with psoriasis (aged > 4 and < 18 years) with either adalimumab 0.8 mg/kg ($n = 38$), 0.4 mg/kg ($n = 39$), or methotrexate ($n = 37$) [147]. After 16 weeks, adalimumab 0.8 mg/kg resulted in significant improvement to PSAI75 (58%) compared with methotrexate (32%) ($p = 0.027$) [147]. All three treatment groups experienced similar AE profiles, with the majority being infections [147].

Ixekizumab is an alternative agent for pediatric psoriasis, with a favorable dosing schedule of every 4 weeks [148]. In a phase III RCT, 171 patients (aged 6 to < 18 years) with moderate-to-severe psoriasis were treated with ixekizumab ($n = 115$) or placebo ($n = 56$). At week 12, 89% of patients on ixekizumab achieved PASI75 compared with 25% of patients on placebo ($p < 0.001$), and 81% of those on ixekizumab achieved static Physicians Global Assessment (PGA) 0/1 compared with 11% on placebo ($p < 0.001$) [148]. At week 48, a treatment response of PASI75 was reported in 103 (90%) and a PGA of 0/1 in 93 (81%) patients ($p < 0.001$). Less than 7% of patients experienced serious AEs, with infections being the most common [148]. Thus, ixekizumab should be considered a second-line treatment.

Ustekinumab was approved for the treatment of moderate-to-severe psoriasis in the pediatric population aged ≥ 6 years [138]. The drug has a favorable dosing schedule of a subcutaneous injection every 12 weeks once the second dose has been given 4 weeks after the first [138]. A phase III RCT evaluated ustekinumab in 110 patients aged 12–17 years [149]. The study evaluated placebo compared with half standard dose (HSD) or standard dose (SD) ustekinumab. The results showed patients achieving PGA 0/1 (HSD 67.6%, SD 69.4%, placebo 5.4%), PASI75 (HSD 78.4%, SD 80.6%, placebo 10.8%), or PASI90 (HSD 54.1%, SD 61.1%, placebo 5.4%) by week 12 ($p < 0.001$) [5, 149]. Furthermore, clinical results were similar to those in adults, with no unexpected AEs [149]. A recent open-label phase III controlled trial evaluated ustekinumab in 44 patients aged 6–12 years. At week 12, a total of 34 (77%; 95% CI 62.2–88.5) patients had achieved PGA 0/1, 37 (84%; 95% CI 69.9–93.4) patients had achieved PASI75, and 28 (64%; 95% CI 47.8–77.6) patients

had achieved PASI90. Ustekinumab was well-tolerated, with clinical responses similar to those in the CADMUS adult study [149, 150]. Limitations included the small population size, which affects the generalizability of the results. Therefore, in pediatric patients with moderate-to-severe psoriasis, ustekinumab should be considered a first-line treatment.

Further controlled trials are underway to evaluate the efficacy and safety of biologics in pediatric patients with psoriasis. In 2020, secukinumab was approved in the EU for pediatric psoriasis (patients aged 6 to < 18 years) [151]. The long-term effects and complications of biologic agents may vary in the pediatric population.

Expert opinion algorithm:

1. Ustekinumab (age ≥ 6 years)
2. Ixekizumab (age ≥ 6 years)
3. Etanercept (age ≥ 4 years)
4. Adalimumab (Europe: age ≥ 4 years)

3.8 Psoriasis in Patients with Childbearing and Breastfeeding Potential

The majority of patients present with psoriasis before the age of 40 years, correlating with the reproductive years [152]. Although half of pregnant patients report clinical improvement in psoriasis, an equal number report a lack of clinical change or worsening [153]. In general, systemic agents such as biologics are not indicated during conception, pregnancy, and breastfeeding as the full safety profile remains unknown because of the lack of evidence and inconsistent data [153, 154]. Discontinuing biologics remains challenging, as cessation can lead to exacerbation of underlying psoriasis [155]. Pre-conception counseling is essential because of the risk of drug-induced teratogenicity [154].

A population-based study by the FDA and the EMA evaluated the prevalence of preterm birth, intrauterine growth restriction (small for gestational age [SGA]), and cesarean section with TNFi ($n = 1027$) or nonbiologic systemic (NBS) treatment ($n = 9399$) during pregnancy [156]. The study was stratified by IBD (CD and UC) and ARTPSO (rheumatoid arthritis, ankylosing spondylitis, PsA, and psoriasis) to compare infliximab, adalimumab, and etanercept. Comparing TNFi and NBS groups, the TNFi group exhibited a higher risk of preterm birth (adjusted odds ratio [aOR] 1.61; 95% CI 1.29–2.02), severely SGA (aOR 1.36; 95% CI 0.96–1.92), and cesarean section (aOR 1.57; 95% CI 1.35–1.82) [156]. The ARTPSO group had a significantly higher risk of preterm birth (aOR 1.42; 95% CI 1.03–1.97), severely SGA (aOR 1.62; 95% CI 1.09–2.41), and cesarean section (aOR 1.57; 95% CI 1.35–1.82) [156]. Furthermore, in ARTPSO, infliximab was associated with a greater risk of preterm birth than were etanercept and adalimumab. Infliximab had a higher prevalence of severe SGA than etanercept and adalimumab in the ARTPSO group. A greater risk of preterm birth was observed in pregnant women who used TNFi therapy in the first trimester [156]. Data from Janssen's global surveillance database indicated that the prevalence of adverse pregnancy and infant (< 2 years) outcomes in the general population was comparable to that with infliximab exposure for numerous conditions [157]. Furthermore, if TNFi are administered during pregnancy, live vaccinations should be withheld in infants within the first 6–12 months of life [158, 159].

The Organization of Teratology Information Specialists (OTIS) analyzed adalimumab in the first trimester of pregnancy in patients with autoimmune conditions and reported a rate of major birth defects of 10% in adalimumab-exposed patients compared with 7.5% in the diseased but unexposed cohort [160]. OTIS did not report significant increases in structural defects, pregnancy complications, or fetal and infant adverse health outcomes, although the risk of preterm delivery increased [160]. FDA information showed active placental transfer of adalimumab during the third trimester and a presence in infants for up to 3 months after birth. However, adalimumab is hypothesized to be safe during breastfeeding because of its large molecule size [136].

Certolizumab pegol has demonstrated no to minimal placental transfer during the last two terms of pregnancy [5, 161, 162]. The lack of an Fc domain, unlike other TNFi, prevents binding to neonatal Fc receptors, minimizing placental transfer [157, 161]. In a prospective pharmacokinetic study of chronic inflammatory diseases, 1 in 14 infants had minimal levels and 13 had no quantifiable levels of certolizumab [161]. Further, at 4 and 8 weeks after delivery, none of the infants had quantifiable levels of the drug, indicating the safety of certolizumab in the third trimester [161]. A chronic inflammatory disease safety database study of 528 pregnancies with maternal exposure to certolizumab did not report an increased risk of teratogenic effect or fetal death compared with the general population [162]. In a pharmacokinetic study of various diseases ($n = 17$), certolizumab was safe during breastfeeding, with minimal transfer to breast milk [163]. Thus, in pregnant and breastfeeding women, certolizumab is a first-line treatment.

Data on the use of ustekinumab and secukinumab in pregnancy are limited [89, 138]. Case reports of five patients with psoriasis treated with ustekinumab demonstrated one first trimester pregnancy loss and four uncomplicated pregnancies [164]. Further, birth defect and pregnancy loss rates were similar to those in non-ustekinumab users in pregnancy. The low transfer rate of ustekinumab in breastfeeding is hypothesized as being due to its large molecular size [165]. Similarly, a secukinumab 7-week follow-up study ($n = 6$) reported an acceptable safety profile but recommended secukinumab only if benefits outweigh risks [89, 166]. Analysis of a secukinumab registry and pooled data

did not find an increased rate of congenital abnormalities or adverse pregnancy outcomes [167, 168]. Thus, secukinumab and ustekinumab are second-line treatments.

Data on brodalumab and ixekizumab in pregnancy are limited. Both IL-17 inhibitors are monoclonal immunoglobulin (IgG) antibodies, which have been known to cross the placenta and be excreted into breast milk [169, 170]. No data on the efficacy and safety of brodalumab in pregnant humans are available [90]. Exposure to ixekizumab was found to have no significant effect on pregnancy outcomes ($n = 58$) in the US PSOLAR (epidemiologic and Psoriasis Longitudinal Assessment and Registries) [171]. Given the limited evidence, brodalumab and ixekizumab are considered last-line treatments.

Research on the use of IL-23 inhibitors in pregnancy is limited. Tildrakizumab, risankizumab, and guselkumab are monoclonal IgG antibodies that can cross the placenta and be transported into human milk during lactation [111–113]. Preliminary data indicate that safety and adverse event profiles are similar to those of older biologic agents [172]. Given the risk of adverse developmental outcomes, IL-23 inhibitors are last-line treatments [172].

Expert opinion algorithm (note that the authors do not fully agree with #2–4 in this treatment algorithm):

1. Certolizumab
2. Ustekinumab or secukinumab
3. Adalimumab, etanercept, or infliximab
4. Ixekizumab, brodalumab, or IL-23 inhibitors

3.9 Patients with Psoriasis and History of Malignancy

Patients with psoriasis are reported to have an increased risk of malignancy, particularly lymphoma and nonmelanoma skin cancer (NMSC) [173–177]. Consequently, age-appropriate routine cancer screening is especially important in patients with psoriasis on immunosuppressive therapies [2].

As TNFi regulate tumor growth factor, concerns remain for malignancy with the use of these drugs [178]. Three meta-analyses and an observational study of multiple conditions, including psoriasis, reported an increased risk of NMSC and/or lymphoma with the use of TNFi [179–182]. The risk of lymphoma (OR 2.14; 95% CI 0.55–8.38) was higher than that of NMSC (OR 1.37; 95% CI 0.59–3.19) in a meta-analysis of rheumatoid arthritis [183]. However, in a large cohort study of various conditions, TNFi did not have a recurrent cancer risk [184].

A pooled analysis of ten controlled trials of secukinumab in psoriasis (n=3430) showed no significant risk of malignancy, with three NMSC cases and no lymphoma cases [133]. Similarly, analysis of safety data from seven controlled trials of ixekizumab in patients with psoriasis ($n = 4209$) reported 27 cases of NMSC and two cases of lymphoma [185]. In a pooled analysis of three RCTs ($n = 4019$) in patients treated with brodalumab, three reported NMSC and two reported lymphomas [186].

Four pooled controlled trials (n=3225) evaluating ustekinumab 45 or 90 mg compared with controls reported 39 cases of NMSC and one case of lymphoma [187]. Given the low risk of NMSC and lymphoma associated with ustekinumab, we recommend this biologic as a first-line treatment [49, 187].

Three cases of NMSC and no lymphoma cases were reported with guselkumab compared with adalimumab and placebo in two psoriasis RCTs [54, 56]. A pooled analysis of two psoriasis RCTs reported 20 cases of NMSC and no cases of lymphoma after 148 weeks of cumulative exposure to tildrakizumab 100 and 200 mg [114]. Furthermore, with risankizumab, the IR of NMSC was 0.3, and no cases of lymphoma were reported [53, 188]. We recommend IL-17 inhibitors and IL-23 inhibitors as second-line treatments in our algorithm.

Expert opinion algorithm:

1. Ustekinumab
2. IL-17 inhibitors or IL-23 inhibitors
3. TNFi in NMSC; avoid TNFi in lymphoma

3.10 Patients with Psoriasis and Coronavirus Disease 2019 (COVID-19)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; coronavirus disease 2019 [COVID-19]) is an evolving health emergency [189]. Although vaccines for COVID-19 are now available, over 2.8 million deaths have occurred globally at the time of writing (https://covid19.who.int/) [189–191]. Despite concerns over increased susceptibility for opportunistic infections, there is limited evidence on the implications of biologic treatments with COVID-19 [192–194]. Withholding biologics and transitioning to safer alternatives may be considered to avoid complications, and initiation of biologic therapy is not recommended in active SARS-CoV-2 infection [195–198]. Moreover, patients should be carefully assessed before a biologic is discontinued because of the risk of diminished treatment response with re-initiation and the development of antibodies, erythroderma, or disease flare [196, 199]. Our treatment algorithm focuses on patients who are negative for COVID-19 and are not at high-risk for SARS-CoV-2 infection.

Two cases have been reported of patients with psoriasis receiving biologics who achieved full recovery from COVID-19 with outpatient supportive therapy [199]. One patient started ustekinumab 3 years prior to COVID-19 diagnosis. These reports should be interpreted with caution as

both patients were aged < 60 years and were without established risk factors for COVID-19 [199].

Presently, clinical data are lacking for the safety of biologic therapy effects with SARS-CoV-2 infections. Analysis of PSOLAR (n = 11,466) showed an overall IR of 1.45 per 100 patient-years for serious infections for biologics and nonbiologics [200]. Pneumonia and cellulitis were the most commonly reported infections, with the following IRs per 100 patient-years for infections: ustekinumab (0.83), etanercept (1.47), adalimumab (1.97), and infliximab (2.49) [200]. The rates of serious infection were lowest for ustekinumab and etanercept and higher for adalimumab and infliximab [200]. A prospective cohort study did not report statistically significant higher infection rates for patients with psoriasis on etanercept (n = 1352), adalimumab (n = 3271), and ustekinumab (n = 994) compared with nonbiologic therapies (n = 3421) [201]. Etanercept (HR 1.10; 95% CI 0.75–1.60) had a higher risk of serious infection than adalimumab (HR 1.26; 95% CI 0.86–1.84) and ustekinumab (HR1.22; 95% CI 0.75–1.99) [201]. In three phase III RCTs in psoriasis (n = 1146), rates of serious infections with certolizumab were comparable to those with placebo [202, 203].

Two phase III RCTs in psoriasis evaluated the role of risankizumab compared with placebo and ustekinumab [53]. Risankizumab had a similar safety profile but superior treatment efficacy to placebo and ustekinumab [53]. Infections were the highest reported adverse event, with less than 3% of treatment groups being affected with serious infections [53]. Analysis of pooled data from three RCTs in psoriasis (n = 2081) showed a lower frequency of infection with tildrakizumab 100 mg (48.9) and 200 mg (52.6) compared with placebo (86) and etanercept (79.5) when adjusted for exposure [52]. Infection rates for guselkumab were similar to those for placebo and adalimumab [54]. As IL-23 inhibitors have low rates of infection compared with TNFi, they are considered first-line treatments in psoriasis and COVID-19. Ustekinumab similarly had low rates of infection so is also a first-line treatment.

Increased levels of IL-17 in acute respiratory distress syndrome have been implicated in lung parenchyma damage and edema through recruiting of neutrophils [204, 205]. Inhibition of IL-17 has potential as a COVID-19 treatment and as a biomarker for lung disease severity [204, 205]. However, prescribing information for secukinumab, brodalumab, and ixekizumab note an increased infection risk [88–90]. RCTs reported an increased risk of upper respiratory tract infection with secukinumab and ixekizumab and a lower risk with brodalumab [204–206]. If severe viral symptoms with high fever develop, clinicians should consider discontinuing biologics [204–208]. Overall, we consider IL-17 inhibitors to be last-line options in our treatment algorithm.

Given the relative novelty of COVID-19, we urge physicians to use our treatment algorithm as a guide. As COVID-19 research is rapidly evolving, therapeutic recommendations should be monitored with vigilance.

Expert opinion algorithm:

1. IL-23 inhibitors or ustekinumab
2. TNFi
3. IL-17 inhibitors

4 Discussion

New RCTs, postmarketing surveillance data, and approval of additional biologic classes have increased the treatment options available for moderate-to-severe psoriasis. This review provides first-line treatment recommendations for managing psoriasis in several clinical scenarios (Table 1).

Since IL-23 inhibitors were recently approved for the treatment of psoriasis, postmarketing trials are needed to confirm their safety and efficacy. Mirikizumab, another IL-23p19 inhibitor, has yet to be approved for psoriasis treatment, but preliminary results are promising [209, 210]. The RCTs OASIS-1 (n = 530) and OASIS-2 (n = 1484) compared mirikizumab with placebo and secukinumab and demonstrated superior efficacy for mirikizumab, with results sustained at week 52 [209–211]. Rates of severe AEs remained < 6% [211]. Recent RCTs have also supported the efficacy of biosimilars compared with originator drugs; however, utilization in the USA has yet to gain momentum [212–216].

A limitation of this article is the potential subjective selection bias for pivotal pertinent articles. Moreover, data from phase III RCTs may be biased because of the selective enrollment criteria. A strength is the breadth of literature included, with a large number of RCTs evaluated.

The indications and limitations of each biologic need to be carefully considered while creating a treatment protocol. As stronger evidence emerges, the treatment algorithm should be modified accordingly.

5 Conclusion

Selection of treatments for moderate-to-severe psoriasis with comorbid conditions is complex and requires careful consideration of numerous factors (i.e., costs, patient preferences, and disease severity). Our algorithms may serve as a guide when choosing a biologic for patients with comorbid PsA, MS, CHF, IBD, hepatitis B, LTBI, lymphoma, NMSC, or COVID-19 or in pregnant or pediatric patients.

Table 1 Biologic therapy algorithm for selecting a psoriasis treatment in individuals with comorbidities or in special populations, based on a review of the current literature

Biologic therapy	Psoriatic arthritis	Multiple sclerosis	Congestive heart failure	Inflammatory bowel disease[a]	Hepatitis B	Latent tuberculosis[b]	Pediatric psoriasis	Childbearing and nursing potential[c]	NMSC and lymphoma	COVID-19
TNF inhibitors										
Adalimumab	First line	Avoid	Avoid[d]	First line (CD and UC)	Third line	Second line	Fourth line (EU: age > 4)	Third line	Third line (NMSC) Avoid (lymphoma)	Second line
Etanercept	First line	Avoid	Avoid[d]	Fourth line	Third line	Second line	Third line (age > 4)	Third line	Third line (NMSC) Avoid (lymphoma)	Second line
Infliximab	First line	Avoid	Avoid[d]	First line (CD and UC)	Third line	Second line	NA	Third line	Third line (NMSC) Avoid (lymphoma)	Second line
Certolizumab pegol	First line	Avoid	Avoid[d]	Second line (CD)	Third line	Second line	NA	First line	Third line (NMSC) Avoid (lymphoma)	Second line
IL-17 inhibitors										
Ixekizumab	First line	First line	First line	Avoid	First line	First line	Second line (age > 6)	Fourth line	Second line	Third line
Secukinumab	First line	First line	First line	Avoid	First line	First line	NA	Second line	Second line	Third line
Brodalumab	NA	First line	First line	Avoid	First line	First line	NA	Fourth line	Second line	Third line
IL-12/23 inhibitors										
Ustekinumab	Third line	Second line	First line	Second line (CD)	Third line	Second line	First line (age > 6)	Second line	First line	First line
IL-23 inhibitors										
Guselkumab	Second line	Third line	First line	Third line	Second line	First line	NA	Fourth line	Second line	First line
Tildrakizumab	NA	Third line	First line	Third line	Second line	First line	NA	Fourth line	Second line	First line
Risankizumab	NA	Third line	First line	Third line	Second line	First line	NA	Fourth line	Second line	First line

CD Crohn's disease, *COVID-19* coronavirus disease 2019, *EU* Europe, *IL* interleukin, *LTBI* latent tuberculosis infection, *NA* not applicable, *NMSC* nonmelanoma skin cancer, *NYHA* New York Heart Association, *TNF* tumor necrosis factor, *UC* ulcerative colitis

[a]Includes CD and UC

[b]Determine LTBI status: if positive, initiate antituberculosis prophylaxis at least 1–2 months prior to biologic therapy

[c]The authors of this article do not fully agree with #2–4 of the treatment algorithm

[d]Contraindicated in NYHA class 3 and 4. Attain baseline echocardiogram in NYHA class 1 and 2. Avoid in patients with ejection fraction < 50%

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Declarations

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