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OPEN REVIEW

Safety of Biologic Agents in the Treatment of Psoriasis Vulgaris: An Integrated Review of Clinical Trials and Real-World Evidence

Psoriasis Vulgaris Tedavisinde Biyolojik Ajanların Güvenliliği: Klinik Çalışmalar ve Gerçek Yaşam Verilerinin Derlemesi

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ABSTRACT
Psoriasis vulgaris is a chronic, immune-mediated inflammatory disease in which dysregulation of the TNF-α and IL-23/Th17 axes drives keratinocyte hyperproliferation and systemic comorbidities. Targeted biologic drugs-TNF-α inhibitors, the IL-12/23 p40 inhibitor ustekinumab, IL-23 p19 inhibitors, and IL-17 pathway inhibitors-successfully control the disease. Network meta-analyses (NMA) demonstrate that these drugs show high efficacy in the short term and are generally well tolerated. Long-term use, however, raises concerns about serious infection, tuberculosis (TB) and hepatitis B virus (HBV) reactivation, malignancy, inflammatory bowel disease (IBD), major adverse cardiovascular events (MACE), and rare paradoxical reactions. This review integrates randomized trial data, long-term extensions, pharmacovigilance signals and real-world cohorts to appraise the safety of biologic agents in psoriasis vulgaris. TNF-α inhibitors carry class-typical risks of serious infection and opportunistic mycoses, particularly in older or comorbid patients, but large registries demonstrate stable long-term profiles when screening and prophylaxis are optimized. Ustekinumab and IL-23 inhibitors show low serious-infection and TB-reactivation rates, reassuring data in patients with prior TB or cancer, and neutral MACE signals. IL-17-pathway inhibitors are associated with predictable, mostly mild mucocutaneous candidiasis and rare IBD onset or exacerbation, with very high skin-clearance rates and durable safety in trials and real-world studies. Observational data suggest that age, baseline comorbidity and concomitant immunosuppression drive absolute risk more strongly than molecule choice. When agents are selected according to comorbidity profile, supported by structured screening, vaccination and close monitoring, modern biologics for psoriasis vulgaris appear broadly safe, with rare but important class-specific adverse events that require proactive counselling and early recognition.

Keywords: Biologics, psoriasis, safety

ÖZET
Psoriasis vulgaris, TNF-α ve IL-23/Th17 yolaklarındaki regülasyonun bozulması sonrası keratinosit hiperproliferasyonuna ve sistemik komorbiditelere yol açan kronik, immün aracılı bir inflamatuar hastalıktır. Biyolojik ajanlar — TNF-α inhibitörleri, IL-12/23 p40 inhibitörü, IL-23 p19 inhibitörleri ve IL-17 yolak inhibitörleri — hastalığı başarılı bir şekilde kontrol eder. Meta-analizler, bu ilaçların kısa vadede yüksek etkinlik gösterdiğini ve genel olarak iyi tolere edildiğini ortaya koymaktadır. Ancak uzun süreli kullanım, ciddi enfeksiyon, tüberküloz (TB) ve hepatit B virüsü (HBV) reaktivasyonu, malignite, inflamatuar bağırsak hastalığı (IBD), majör advers kardiyovasküler olaylar (MACE) ve nadir paradoksal reaksiyonlar konusunda endişelere yol açmaktadır. Bu derleme, psoriasis vulgaris'te biyolojik ajanların güvenliğini değerlendirmek için randomize çalışma verilerini, uzun vadeli uzatma çalışmalarını, farmakovijilans sinyallerini ve gerçek yaşam verilerini bir araya getirmektedir. TNF-α inhibitörleri, özellikle yaşlı veya komorbid hastalarda, ciddi enfeksiyon ve fırsatçı mikozlar gibi sınıfa özgü riskler taşır, ancak büyük kayıtlar, tarama ve profilaksi ile uzun vadede stabil bir profile sahip olduğunu göstermektedir. Ustekinumab ve IL-23 inhibitörleri, düşük ciddi enfeksiyon ve TB reaktivasyon oranları, önceden TB veya kanser öyküsü olan hastalarda güven verici veriler ve nötr MACE sinyalleri göstermektedir. IL-17 yolak inhibitörleri, öngörülebilir, çoğunlukla hafif mukokutanöz kandidiyazis ve nadir IBD başlangıcı veya alevlenmesi ile ilişkilidir ve klinik çalışmalar ve gerçek yaşam çalışmalarında çok yüksek deri temizlenme oranları ve kalıcı güvenlik göstermiştir. Gözlemsel veriler, yaş, başlangıçtaki komorbidite ve eşlik eden immünosupresyonun, molekül seçiminden daha güçlü bir şekilde mutlak riski etkilediğini göstermektedir. Komorbidite profiline göre, yapılandırılmış tarama, aşılama ve yakın izlem ile desteklenen ajanlar seçildiğinde, psoriasis vulgaris için biyolojik ilaçlar genel olarak güvenli görünmektedir, ancak proaktif danışmanlık ve erken tanı gerektiren nadir ancak önemli sınıfa özgü advers olaylar mevcuttur.

Anahtar Kelimeler: Biyolojikler, psoriasis, güvenlilik

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INTRODUCTION

Psoriasis vulgaris is a chronic, immune-mediated dermatosis characterized by dysregulated TNF-α and IL-23/Th17 signalling (1). This inflammatory cascade drives keratinocyte proliferation and a systemic inflammatory milieu that underlies cardiometabolic, hepatic and psychological comorbidities (2). Targeted biologic therapies have reshaped the management of moderate-to-severe disease, achieving rapid and durable PASI 90–100 responses in many patients who previously had refractory disease or unacceptable toxicity on conventional systemic agents.

Randomized trials and network meta-analyses consistently show that IL-17 and IL-23 inhibitors achieve the highest short-term clearance rates, with TNF-α inhibitors and ustekinumab somewhat less efficacious but still superior to traditional systemic treatments (3-5). However, trial populations are relatively young, carefully screened and followed for limited periods. Contemporary practice extends biologic treatment to older, multimorbid patients with long-standing systemic inflammation, prior malignancy or chronic viral infections—populations in whom long-term safety is a central concern (6-8).

Key safety questions:

- How do biologic classes differ regarding serious infection, opportunistic mycoses and viral reactivation (HBV, TB)?
- Is there a meaningful difference in MACE or cerebrovascular risk between classes or individual agents?
- What is the real-world risk of IBD, paradoxical reactions or rarely seen adverse events such as bullous pemphigoid?
- If biologics may be safely prescribed in patients with previous malignancy, chronic viral hepatitis, TB or HIV infection, or in paediatric and elderly populations?

This review synthesizes randomized trials and real-world evidence across biologic classes used in psoriasis vulgaris. Within each class, we summarize class-level safety themes and then highlight drug-specific data, with a particular focus on long-term extensions, pharmacovigilance analyses and special populations.

TUMOUR NECROSIS FACTOR-ALPHA (TNF-α) INHIBITORS

Class overview

TNF-α is a critical pro-inflammatory cytokine for host defence against intracellular pathogens and a central driver of many autoimmune and autoinflammatory diseases, which makes TNF-α inhibitors cornerstone therapies in several difficult-to-treat conditions but also links their use to an increased risk of infections (9). A systematic review and meta-analysis of 29 randomized controlled trials (RCTs) also including psoriasis patients found that treatment with TNF-α antagonists nearly doubles the risk of active tuberculosis compared with placebo or standard care, with particularly elevated risk in rheumatoid arthritis and in high TB-incidence regions (10). A systematic review of fungal infections associated with TNF-α inhibitors identified invasive and opportunistic mycoses-particularly histoplasmosis, coccidioidomycosis and cryptococcosis—occurring predominantly in patients treated with infliximab and adalimumab, often in endemic areas or in the presence of additional immunosuppressive drugs (9).

TNF-α inhibitors are the most-studied biologics regarding HBV reactivation. In psoriasis and other IMID cohorts, HBsAg-positive patients exposed to anti-TNF without antiviral prophylaxis have reported reactivation rates around 14–63%, whereas HBsAg-negative/anti-HBc-positive patients carry a lower 3–5% risk that is usually manageable with close monitoring (11). In older adults with psoriatic disease, a large population-based cohort found similar rates of serious infection with TNF inhibitors compared with methotrexate and other traditional systemics, while IL-12/23 and IL-23/17 biologics were associated with lower rates of serious infection; in contrast, the JAK inhibitor tofacitinib carried the highest infection risk (8). TNF-α inhibitors have a complex relationship with congestive heart failure (CHF). In a pivotal RCT of infliximab in patients with advanced CHF (NYHA III–IV, LVEF <35%), high-dose infliximab (10 mg/kg) increased the risk of hospitalization or death versus placebo. Multiple case reports across infliximab, adalimumab and certolizumab pegol describe new-onset or worsening CHF and, rarely, sudden death temporally related to treatment, whereas small studies with etanercept have suggested possible improvements in ventricular function and symptoms. In practice, TNF inhibitors are generally contraindicated in patients with NYHA III–IV CHF or LVEF <50%, and baseline echocardiography plus cardiology input is advised before considering TNF blockade in those with milder (NYHA I–II) heart failure (12).

Beyond heart failure, TNF-α inhibitors may modestly increase MACE. In a large network meta-analysis of 40 comparative studies (126,961 patients), anti-TNF agents were associated with a higher MACE risk versus placebo (13). With respect to malignancy, long-term TNF-α blockade raises theoretical concerns because of impaired immune surveillance and the complex role of TNF-α in tumorigenesis, but current clinical data are largely reassuring. The most consistent signal is a modestly increased risk of non-melanoma skin cancer, whereas a recent large patient-level meta-analysis of 45 interventional and 10 observational studies across all approved TNF inhibitors did not demonstrate a statistically significant increase in overall cancer risk (excluding NMSC), although a trend with longer exposure and possible lymphoma excess was noted and confounded by underlying disease and co-medication (14). Paradoxical immune-mediated events are a distinctive feature of the TNF-α inhibitor class. The most frequent are psoriasiform paradoxical reactions, with an estimated incidence of about 3.8–10.7% among treated patients. Infliximab accounts for roughly half of reported cases, followed by adalimumab and etanercept, whereas certolizumab and golimumab are rarely implicated. Reactions may present as de novo psoriasis, flares or phenotype switches in patients treated for psoriasis, and typically mimic plaque or palmoplantar pustular disease, although guttate, inverse, generalized pustular and alopecic variants are also described. Onset is highly variable (from <1

month to >10 years; mean ≈16 months), and most eruptions improve or resolve after TNF-α inhibitor withdrawal, with milder cases sometimes manageable using topical therapy or switching to another biologic class (15).

Less common but clinically important paradoxical events include lupus-like and sarcoidosis-like syndromes and other granulomatous eruptions. Lupus-like reactions have low incidence (≈0.06–0.18% depending on the agent) and are most often linked to infliximab, adalimumab and etanercept; they range from isolated cutaneous lupus to full systemic lupus erythematosus, usually with ANA positivity and onset around 1–1.5 years after starting therapy, and generally regress after drug discontinuation, though some patients require ongoing lupus-directed treatment. Sarcoidosis-like disease is still rare (≈0.04%), occurs predominantly with etanercept, and may involve skin, lungs and, less often, heart; most cases show at least partial improvement after stopping the TNF-α inhibitor and initiating corticosteroids (15). TNF-α inhibitors have been linked to demyelinating disease. In a phase I infliximab trial in rapidly progressive multiple sclerosis (MS), cerebrospinal fluid leukocytes and immunoglobulins rose after treatment, suggesting TNF neutralization exacerbated disease activity. Multiple case reports describe new-onset or worsening MS in patients receiving etanercept, infliximab or adalimumab for psoriasis or psoriatic arthritis, with neurological symptoms often improving after drug withdrawal. On this basis, TNF-α inhibitors are generally avoided in patients with established demyelinating disease and used with great caution in those with suggestive neurological histories (12).

Adalimumab

Among TNF-α inhibitors, adalimumab remains one of the most widely used biologics in dermatology, and available real-world data support a safety profile broadly consistent with the TNF class. A retrospective single-centre cohort from Italy including both paediatric and elderly patients with psoriasis treated with originator adalimumab and its biosimilar SB5, as well as etanercept biosimilar SB4, showed that these agents were effective and generally well tolerated across age groups, with no new safety signals emerging over follow-up; adverse events were mostly mild and led to few discontinuations (16). Beyond psoriasis, a large series of hidradenitis suppurativa cases from a Turkish dermatology clinic specifically evaluated the risks of hepatitis B and tuberculosis reactivation during adalimumab treatment: Among patients at risk for HBV or TB reactivation who received appropriate antiviral (entecavir or tenofovir) or isoniazid prophylaxis, no cases of HBV or TB reactivation were observed during treatment. This highlights the importance of systematic baseline screening and prophylaxis (17).

A nationwide retrospective cohort study using Taiwan's National Health Insurance database compared the risk of herpes zoster across multiple biologics and traditional systemic treatments; in this analysis, adalimumab was associated with a significantly increased risk of herpes zoster relative to traditional systemic therapies (18). A recent systematic review and meta-analysis of randomised psoriasis trials found no significant increase in MACEs with TNF-α inhibitors, IL-17, IL-12/23 or IL-23 inhibitors compared with placebo, suggesting that cardiovascular risk under adalimumab is driven primarily by traditional risk factors rather than the biologic itself (19).

Etanercept

The OBSERVE-5 post-marketing registry followed 2510 psoriasis patients on etanercept for up to five years, observing cumulative incidences of 6.5% for serious infection and 3.2% for malignancy excluding non-melanoma skin cancer, with event rates comparable to administrative claims data and no new safety signals (20). Psoriasis severity and quality of life improved and remained stable. In a 30-month prospective cohort directly comparing adalimumab, infliximab, etanercept, secukinumab and ustekinumab, etanercept was associated with musculoskeletal and reproductive adverse events (e.g. menstrual disorders) but did not show higher serious adverse event or discontinuation rates; overall, ustekinumab had the most favourable safety profile, while infliximab and adalimumab had more frequent adverse events (AEs) (21).

Infliximab

Infliximab provides rapid disease control but has distinct safety considerations. A detailed review of infliximab and its biosimilars in psoriasis and other indications emphasized infusion reactions, immunogenicity and loss of response as key long-term challenges (22). The same 30-month observational cohort noted higher rates of asymptomatic liver enzyme elevation, fatigue and respiratory infections with infliximab compared with other biologics (21). These findings underscore the need for early vigilance, careful patient selection and reconsideration of long-term infliximab therapy when safer alternatives are available.

Certolizumab pegol

Certolizumab pegol, a pegylated Fab fragment lacking the Fc region, has minimal placental transfer and is generally preferred in women planning pregnancy and breastfeeding. A prospective, non-interventional 1-year real-world study (CIMREAL) in 399 plaque psoriasis patients reported PASI75 and PASI90 response rates of 77% and 56.5% at 12 months, with marked DLQI improvement; 30.6% experienced AEs and 9.3% serious AEs, but no new safety signals emerged (23). Pharmacovigilance analyses in pregnant women with psoriasis suggest broadly similar maternal and neonatal outcomes across TNF inhibitors, with spontaneous abortion the most common event; certolizumab's safety profile overlapped with other TNF inhibitors, emphasizing that current pregnancy recommendations—largely based on preclinical data—should be continually updated using real-world evidence (24). FAERS-based analyses of certolizumab confirm expected infection and musculoskeletal AEs and identify rare unexpected events such as pemphigus and basal cell carcinoma, warranting continued surveillance but not altering its general safety profile (25).

IL-12/23 (p40) Inhibition

Ustekinumab

Ustekinumab targets the p40 subunit shared by IL-12 and IL-23, modulating both Th1 and Th17 pathways. Network meta-analyses place ustekinumab among biologics with

high short-term efficacy and favourable tolerability (3,4). In an updated network meta-analysis of 62. RCTs including 11 biologics, ustekinumab clustered with agents combining high PASI90 rates and low withdrawal due to AEs (4). The observational cohort comparing TNF inhibitors, secukinumab and ustekinumab found that ustekinumab had the lowest incidence of adverse events overall, reinforcing its reputation as a "steady and safe" option, especially in patients with multiple comorbidities (21).

Bullous pemphigoid induced by biologics (BIBP) is a rare but serious dermatologic adverse event. A systematic review identified 15 cases of BIBP in psoriasis patients, with ustekinumab accounting for six, mostly in individuals previously exposed to TNF inhibitors. Latency tended to be longer with ustekinumab than with TNF blockers, and causality assessments rated most cases as "probable". Awareness of this entity and baseline history of bullous disease are important when selecting therapy and managing new blistering eruptions (26)

IL-23 (P19) INHIBITORS

Class overview

IL-23 p19 inhibitors selectively modulate the Th17 axis while sparing IL-12, potentially preserving some host defence and antitumour surveillance. Trials and real-world studies consistently report low rates of serious infection, TB reactivation and malignancy, including in patients with prior TB infection (27-29). A monocentric study of 16 psoriasis patients with prior TB infection (positive Quantiferon) treated with guselkumab, risankizumab or tildrakizumab found that all achieved at least PASI75, most PASI100, and none developed TB reactivation over a median 18.8-month follow-up, regardless of whether they received isoniazid prophylaxis (27). These findings support IL-23 inhibitors as preferred options in patients with TB infection when anti-TNF therapy is relatively contraindicated. Real-world data on HBV reactivation with IL-23 (p19) inhibitors are still limited but currently reassuring. In a retrospective cohort of 219 psoriasis patients treated with newer biologics (including guselkumab and risankizumab), 21% were anti-HBc IgG–positive and thus at risk, yet among the 40 who received antiviral prophylaxis no HBV reactivation or clinically relevant ALT/AST elevation occurred during follow-up (30).

Real-world data suggest a potentially favorable cardiovascular profile for IL-23 (p19) inhibitors. In a large TriNetX cohort of >12,000 biologic-treated psoriasis patients, biologics overall were associated with a lower 5-year risk of MACEs compared with oral systemic therapies. Within class-specific analyses, patients receiving only anti-IL-23 agents also showed a significantly reduced risk of any cardiovascular disease versus oral drugs, supporting the hypothesis that effective IL-23 blockade may attenuate systemic vascular inflammation (31). Across placebo-controlled trials and long-term extension studies, IL-23 (p19) inhibitors have not been associated with an increased risk of malignancy. In a large meta-analysis, short-term randomized data showed no excess malignancy with IL-23 blockers compared with placebo (RR ≈0.87), and pooled long-term exposure-adjusted incidence rates remained low, around 0.40/100 patient-years for non-melanoma skin cancer and 0.43/100 patient-years for malignancies excluding non-melanoma skin cancer, without evidence of a time-dependent increase. Overall, current data support a favorable malignancy profile for guselkumab, risankizumab and tildrakizumab, although continued pharmacovigilance and age- and risk-appropriate cancer screening remain advisable (32).

Case series in HIV-positive patients showed good disease control without deterioration in viral load or CD4 counts under guselkumab or risankizumab, suggesting that IL-23 inhibitors may be appropriate with infectious-disease oversight (33). Drug-survival reviews highlight IL-23 inhibitors as the class with the highest long-term persistence, likely reflecting a combination of high efficacy, convenient dosing and favourable safety (34).

Guselkumab

Real-world cohorts in Asia confirm guselkumab's sustained efficacy and quiet safety profile. In a Chinese single-centre study (mean follow-up ~72 weeks, n=37), over 80% of patients achieved PASI90–100 between weeks 60–92 with no serious AEs; abnormal HBV markers were common but no HBV or TB reactivation occurred (28). A 20-week interim analysis of a 52-week Japanese post-marketing surveillance program (n=411) reported adverse drug reactions(ADRs) in 6.6% and serious ADRs in 2.2% of patients, mostly infections such as nasopharyngitis, with significant early PASI improvement (29). Switching studies provide further reassurance. A three-year Italian multicentre study of 169 patients who partially responded to ustekinumab and switched to guselkumab found PASI75/90/100 rates of 88.4%, 55.8% and 32.6%, respectively, at three years, with no severe AEs (35). Another two-year real-life study of 61 patients who had failed at least one IL-17 inhibitor showed that guselkumab maintained high PASI90/100 rates and improved difficult-to-treat areas, again without severe AEs (36).

Risankizumab

Risankizumab has robust long-term data. The LIMMitless phase 3 open-label extension followed psoriasis patients for up to six years, showing sustained PASI90/100 responses and low, stable rates of serious infection, malignancy and MACE (37). Real-world 24-week and longer-term series confirm high effectiveness and a reassuring safety profile across naive and biologic-experienced patients, including those with cardiometabolic comorbidities (38-40). In three-year retrospective study (n=333), risankizumab efficacy and AE rates were similar in patients with and without cardiometabolic disease, with no major safety concerns (40). In very severe psoriasis (baseline PASI ≥30, difficult areas), the VESPA real-life study demonstrated that risankizumab achieved sustained PASI75/90/100 and DLQI improvement up to 104 weeks without new safety signals (39). Post-marketing pharmacovigilance has generated important-but as yet unconfirmed-signals. A FAERS disproportionality analysis suggested a potential cerebrovascular accident (CVA) signal for risankizumab compared with other psoriasis therapeutics (41). Further

FAERS mining identified unexpected AEs such as myocardial infarction, pancreatitis, diabetes and nephrolithiasis, but most signals were weak and tended to occur early in treatment (42). EudraVigilance data highlight serious reports mainly in the categories of infections, malignancy, nervous-system and cardiac disorders, aligning with known risks and underlining the need for continued surveillance (43).

These hypotheses have been challenged by letters emphasizing the limitations of spontaneous reporting, lack of a plausible mechanism linking IL-23 blockade to CVA and reassuring long-term trial event rates compared with epidemiologic benchmarks (44). A retrospective study of coagulation parameters in patients treated with risankizumab or guselkumab found no evidence of hypercoagulability, whereas secukinumab modestly shortened PT, the clinical significance of which remains uncertain (45).

Tildrakizumab

In elderly psoriasis patients with difficult areas, the ESTER multicentre real-life study (n=49, mean age 73 years) found that 77.5%, 60% and 45.2% achieved PASI75/90/100 at week 28, with substantial improvement in scalp, genital and palmoplantar disease and no geriatric-specific safety signal (46). A phase 4 open-label real-world trial up to 64 weeks reported PASI75/90/100 rates of 87/56.5/32.6% at week 52, with no tildrakizumab-related serious AEs (47). A phase 3b RCT in scalp psoriasis confirmed sustained efficacy through week 52 with no treatment-related serious AEs (48).

IL-17-PATHWAY INHIBITORS

Class overview

IL-17 inhibitors are highly effective biologic agents that target the IL-23/Th17 axis, a central pathway in the pathogenesis of psoriasis, by blocking IL-17A, IL-17A/F, or the IL-17 receptor. Agents such as secukinumab, ixekizumab, bimekizumab, and brodalumab provide rapid and sustained skin and joint clearance and are now widely used for moderate-to-severe disease. Short-term NMAs consistently rank them among the most efficacious agents, albeit with somewhat higher AE rates than IL-23 inhibitors (3,4). A Polish real-world comparison of bimekizumab, secukinumab and ixekizumab in 98 patients showed that all three improved PASI rapidly and all agents showing favourable safety with no serious AEs (49). A large multicentre retrospective study of 405 psoriasis patients with latent TB infection treated with IL-17 or IL-23 inhibitors found only one case of active TB, in a patient on ixekizumab who had not received chemoprophylaxis; no reactivations occurred in the remaining patients during a mean follow-up of about 33 months. The overall TB reactivation rate was 0.46% for IL-17 inhibitors and 0% for IL-23 inhibitors, with no significant difference between the two classes (50).

A recent systematic review and meta-analysis of patients with PsA showed that IL-17 inhibitors carry a measurable but overall low risk of HBV reactivation, with a pooled reactivation rate around 4% across HBV serotypes and no clear difference from other targeted agents. Reactivation risk is strongly driven by HBV status: in chronic HBV infection, rates reached roughly 20–30% when IL-17 inhibitors (especially secukinumab) were used without antiviral prophylaxis, whereas no reactivations were observed in chronic carriers who received concomitant antiviral prophylaxis (51). Experimental data suggest that IL-17A has a complex role in atherosclerosis: blockade of IL-17A reduces plaque burden and vascular inflammation in mouse models, implying a pro-atherogenic effect, whereas other studies indicate, potentially plaque-stabilising actions. Clinically, however, a systematic review and meta-analysis of nine RCTs found no significant change in MACE risk with IL-17 inhibitors overall, nor in secukinumab or ixekizumab subgroups, and no dose-response signal (52).

Current evidence suggests that IL-17 inhibitors have a very favorable malignancy profile, with overall cancer rates similar to or even lower than those of the general population and anti-TNF–treated patients. Large cohorts and meta-analyses report very low incidence rates of melanoma and non-melanoma skin cancer, without a consistent signal for increased internal malignancies. Some population-based data even suggest a reduced risk of certain tumors, including non-Hodgkin lymphoma, colorectal, hepatobiliary, ovarian cancers, melanoma and basal cell carcinoma in patients receiving IL-17 inhibitors, although follow-up remains relatively short and ongoing surveillance is warranted (53). IL-17 is crucial for mucocutaneous antifungal immunity. A large multi-source observational study (WHO and EMA safety databases, national prescription registry, psoriasis cohort) demonstrated a strong association between IL-17 inhibitors and candidiasis, especially oropharyngeal and esophageal disease; risk was 2–42-fold higher compared with TNF inhibitors, though most cases were non-invasive and managed effectively with antifungals (54).

IL-17 inhibition has also been linked to potential IBD new onset or exacerbation. A systematic review and meta-analysis of IL inhibitors in psoriasis found no significant increase in new-onset IBD with most agents, but ixekizumab was associated with a small but statistically significant excess risk, prompting calls for heightened vigilance in high-risk patients (55). Paradoxical eczema is an emerging safety issue across IL-17 inhibitors. In a series of 595 IL-17-treated psoriasis patients, 25 (4.2%) developed paradoxical eczema-most commonly atopic dermatitis-like-often in patients with atopic background and elevated IgE. Eczematous reactions were milder with secukinumab and more severe with bimekizumab; IL-17 inhibition was withdrawn in all cases requiring specific treatment. Severe cases responded rapidly to short courses of oral JAK inhibitors (upadacitinib or abrocitinib), after which patients were switched successfully to IL-23 inhibitors without relapse (56).

Secukinumab

Secukinumab and ixekizumab selectively inhibit IL-17A. Real-world data suggest that secukinumab can be used safely in patients with latent TB when proper screening and, often, prophylaxis are applied. In a multicentre Italian cohort of 59 psoriasis patients with latent TB, ten (17%) patients did not undergo prophylaxis before starting secukinumab, 83.1% received isoniazid ± rifampicin prophylaxis; after a mean of

84 weeks of secukinumab, no TB reactivation or unexpected safety signals were observed (57). Another case documented simultaneous HBV reactivation and hair discoloration under secukinumab in a patient with anti-HBcIgG positivity; HBV DNA became detectable despite normal transaminases and negative HBsAg, and entecavir therapy cleared viremia while hair discoloration persisted. The authors stressed serial HBV DNA monitoring in anti-HBcIgG-positive patients lacking prophylaxis (58).

Paradoxical phenomena such as Behçet-like disease can be seen with IL-17 inhibitors. A case report plus literature review described a psoriasis patient who developed Behçet-like disease (oral/genital ulcers, nodular lesions) after secukinumab, with resolution after drug discontinuation and highlighting similar cases across IL-17 inhibitors (59).

Overall, secukinumab remains a highly effective agent whose infectious and paradoxical risks are largely manageable with appropriate pre-treatment assessment and multidisciplinary follow-up.

Ixekizumab

Long-term real-world data for ixekizumab have recently expanded and strongly support its durability of response and reassuring safety profile. In the large IL PSO multicentre retrospective study, 1096 patients with moderate-to-severe plaque psoriasis treated with ixekizumab for at least one year achieved PASI 90 and PASI 100 responses of 85.0% and 69.1% at week 52; among the 145 patients completing five years of therapy, PASI 90 and complete skin clearance were maintained without the emergence of new safety signals (60). These findings confirm that the high clearance rates seen in randomized trials can be sustained over many years in routine practice, including in patients with prior biologic exposure and challenging disease distributions. The class-typical risk of mucocutaneous candidiasis with IL-17 blockade has been quantified in an integrated safety analysis of 25 ixekizumab clinical studies across psoriasis, psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) (61). Candida infections occurred at low incidence rates—1.9, 2.0 and 1.2 per 100 patient-years in PsO, PsA and axSpA, respectively—and were predominantly single, mild-to-moderate episodes affecting the oral or genital mucosa. Most events resolved with topical antifungals or even without specific therapy, and virtually none led to treatment discontinuation, indicating that candidiasis with ixekizumab is usually manageable and non-invasive. Importantly, no unexpected invasive fungal patterns emerged despite extensive cumulative exposure.

A recent systematic literature review, which complements these datasets and includes 118 real-world publications, reported that ixekizumab is consistently effective in psoriasis, PsA, and axSpA, achieving high drug survival rates and meaningful improvements in the Dermatology Quality of Life Index. It also reported that ixekizumab frequently outperformed comparator biologics in achieving DLQI 0/1 and that no unexpected safety signals were identified (62). Across studies, the safety profile remained aligned with clinical-trial experience, with no new serious-event signals identified. Taken together, these real-world data position ixekizumab as a high-efficacy IL-17A inhibitor with durable responses, low rates of mostly mild mucocutaneous candidiasis and a stable long-term safety profile that is comparable to, or in some domains favourable over, other agents within the IL-17 class.

Brodalumab

Brodalumab, an IL-17 receptor A antagonist, initially raised concern due to imbalances in suicidal ideation/behaviour (SIB) in early trials. A recent synthesis of open-label and real-world studies, however, found that most AEs mirrored the package insert (upper respiratory tract infection, injection-site reactions), serious infections were rare, and there was no clear excess of completed suicides versus background psoriasis risk (63). Several studies comparing brodalumab with other biologics reported no increase in MACE or serious fungal infections (63). Current practice emphasises routine mood screening and psychiatric collaboration where indicated, rather than blanket avoidance.

Bimekizumab

Bimekizumab neutralizes both IL-17A and IL-17F. Network meta-analyses and head-to-head trials show that it can induce PASI100 more frequently than IL-17A-only inhibitors and some IL-23 inhibitors in the short term (64). Longer-term data are now available. In the BE RADIANT phase IIIb trial, bimekizumab was superior to secukinumab for PASI100 at year 1; over three years, PASI100 responses were maintained in ~69% of patients initially randomised to bimekizumab, and in those switched from secukinumab, with stable rates of nasopharyngitis, oral candidiasis and upper respiratory tract infection and no increase in serious infections, IBD or suicidality over time (65). A safety-focused narrative review of bimekizumab concluded that although mucocutaneous candidiasis is more frequent than with other IL-17 inhibitors, events are typically mild to moderate, respond to azoles and rarely require discontinuation; serious infections, malignancies and MACE have been uncommon in trials and extensions (66).

CROSS-CLASS SAFETY THEMES AND SPECIAL POPULATIONS

HBV and TB reactivation

Multiple studies converge on a key principle: risk is highest with TNF inhibitors but can be mitigated by systematic screening and prophylaxis. HBV reactivation risk under IL-17 and IL-23 inhibitors appears low but not negligible in anti-HBcIgG-positive patients without prophylaxis, as illustrated by the secukinumab-related case (58) and dermatology HBV cohorts in psoriasis and HS (17,30). IL-23 inhibitors have reassuring data in TB-infected patients, with no reactivation seen across clinical trials and real-world cohorts when active disease is excluded and prophylaxis used selectively (27-29).

Malignancy and oncologic patients

Retrospective series of psoriasis patients with prior or concomitant malignancy treated with biologics suggest that IL-23 and IL-17 inhibitors—followed by ustekinumab—can be used safely with oncology input, without obvious increases in recurrence or new cancer events during follow-up (6,7). IL-23 and IL-17 blockade may be less broadly immunosuppressive

than TNF inhibition, although definitive comparative oncologic safety data are lacking. Current practice favours IL-23 or IL-12/23 agents when comorbid psoriasis emerges as an immune-related adverse event during checkpoint inhibitor therapy, as they allow continued oncologic treatment (6).

Cardiovascular events

Psoriasis is associated with increased rates of ischemic heart disease and heart failure, so cardiovascular status should be systematically assessed before and during biological therapy. A comprehensive meta-analysis of 43 RCTs involving TNF, IL-17, IL-12/23 and IL-23 inhibitors found no significant increase in MACE risk for any biologic class compared with placebo (19). In contrast, TNF inhibitors have been linked to new-onset or worsening congestive heart failure, particularly in patients with NYHA class III–IV disease, and are generally avoided in this setting, with a preference for alternative biologic classes. For patients with stable ischemic heart disease or compensated heart failure, biologics, including TNF inhibitors, can usually be used, but treatment should be individualized with cardiology consultation, optimization of traditional cardiovascular risk factors, and regular follow-up as part of comprehensive psoriasis management.

Inflammatory bowel disease and gastrointestinal safety

A systematic review/meta-analysis of new-onset IBD in psoriasis patients receiving IL inhibitors (bimekizumab, ixekizumab, secukinumab, brodalumab, ustekinumab) across 21 RCTs identified 22 IBD cases in active-treatment arms versus one in controls; only ixekizumab showed a statistically significant risk difference. For bimekizumab, secukinumab, brodalumab and ustekinumab, the data did not support a significantly increased risk compared with placebo or non-IL biologics (55). Clinically, IL-23 inhibitors are generally preferred in patients with pre-existing IBD, while IL-17 inhibitors can still be considered in carefully selected cases with gastroenterology oversight.

Paediatric and elderly patients

Biologics are increasingly used in paediatric psoriasis. A structured review of biologics in children found encouraging efficacy and favourable short-term safety across TNF, IL-12/23 and IL-17 agents, with signals that IL-12/23 and IL-17A inhibitors may be more efficacious than TNF inhibitors, though long-term paediatric safety data remain limited (67). Anti-TNF biosimilar experience in children and older adults similarly suggests good tolerability with careful monitoring (16). In older adults, the Ontario cohort showed that IL-12/23, IL-23 and IL-17 biologics were associated with a lower rate of serious infection than traditional systemic agents, whereas TNF inhibitors had similar infection rates to methotrexate (8). IL-23 inhibitors such as tildrakizumab and guselkumab have especially reassuring geriatric data (28,46).

Rarely seen adverse events

IL-17 inhibitors may cause paradoxical eczema, Behçet-like disease, and rarely vasculitic phenomena; in most cases, discontinuation of the drug is sufficient, and paradoxical eczema responds to short-term systemic immunomodulatory therapy such as JAK inhibitors, after which switching to IL-23 is usually successful. (56,59). Bullous pemphigoid induced by biologics, most commonly ustekinumab and TNF inhibitors, is rare but important (26).

Herpes zoster risk may differ between agents, with adalimumab carrying higher risk and ustekinumab/guselkumab possibly lower compared with traditional systemics, though vaccination with recombinant zoster vaccine remains advisable for most patients initiating biologic therapy (18).

CONCLUSION

Taken together, randomized trials, long-term extensions, pharmacovigilance analyses and real-world cohorts provide a broadly reassuring picture of biologic safety in psoriasis vulgaris. TNF inhibitors retain a central role but require the greatest vigilance for TB, HBV and opportunistic mycoses. Ustekinumab offers steady long-term tolerability, while IL-23 inhibitors combine excellent efficacy with low serious-infection and TB-reactivation rates, neutral MACE signals and good performance in cancer survivors, TB-exposed and elderly patients. IL-17-pathway inhibitors deliver very rapid, deep skin clearance at the cost of predictable mucocutaneous candidiasis and rare paradoxical or IBD-related events, which are usually manageable with early recognition and appropriate switching.

Ultimately, absolute risk is driven more by age, comorbidities and concomitant immunosuppression than by any single biologic agent. Aligning drug choice with each patient's risk profile, supported by structured screening, vaccination and close monitoring, allows clinicians to exploit the remarkable efficacy of modern biologics while minimizing preventable harm (Table 1-2).

Table 1. Practical Prevention and Monitoring

Pre-treatment screening	IGRA/TST with chest imaging as indicated; HBV/HCV serology (with hepatology input for anti-HBcIgG-positive or HBsAg-positive patients); HIV testing where risk factors exist; baseline cancer and IBD history.
Vaccination	Update influenza, pneumococcal and recombinant zoster vaccines before or early during therapy; avoid live vaccines during active biologic treatment.
On-treatment monitoring	Regular clinical review, targeted lab monitoring (liver function, HBV DNA where relevant), vigilance for signs of infection, new GI symptoms, neurologic deficits, unexplained lymphadenopathy or blistering eruptions.

IGRA: Interferon Gamma Release Assay, TST: Tuberculin skin test, IBD: Inflammatory bowel disease, GI: Gastrointestinal,

Table 2. Class selection by comorbidity

Prior TB infection	Consider IL-23 or IL-12/23 inhibitors over TNF inhibitors (27).
Chronic HBV	Any biologic requires hepatology-supervised prophylaxis; case data suggest IL-17 and IL-23 inhibitors are reasonable with entecavir/tenofovir in at-risk patients (17,30,58).
IBD	Consider IL-23 or TNF inhibitors; avoid IL-17 inhibitors in active IBD when alternatives exist (55).
Prior malignancy	In patients with a current or recent (≤5-year) history of malignancy, IL-17 or IL-23 inhibitors should generally be preferred as first-line biologics, while TNF-α inhibitors and ustekinumab may be considered on an individual basis in close collaboration with oncology.
Pregnancy/lactation	Consider certolizumab when TNF inhibition suffices (23,24).

IL: Interleukin, TNF: Tumour Necrosis Factor, IBD: Inflammatory bowel disease,

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