Psoriasis: Targets and Therapy

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REVIEW

Infection Risk and Vaccination in the Management of Psoriasis: Considerations for Biologic Therapy

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Abstract: This narrative review examines critical considerations for biologic treatment in psoriasis patients, with a focus on infection risks, providing current recommendations and practical considerations for prevention, including vaccination, screening, and management strategies. Since type I (Th1) inflammation and type III (Th17) inflammation protect against intracellular and extracellular infections, respectively, it is logical that biologic treatments blocking these pathways may be associated with an increased risk of infection. It has been proven that TNF inhibitors are associated with an increased risk of latent tuberculosis (LTBI) and hepatitis B virus reactivation. However, not all biologics exert the same immunosuppressive effect, as IL-17 and IL-23 inhibitors may be associated with a lower risk of infection. In general, pre-treatment screening for reactivable infectious diseases is advised for all patients initiating biologic therapy. Vaccination schedules for patients with psoriasis under biologic treatment should mirror those of the general population, including annual influenza and COVID-19 vaccines. Live-attenuated vaccines are generally advised against in patients undergoing biologic treatment. However, some live-attenuated vaccines may be safely administered under specific circumstances with IL-17 or IL-23 inhibitors. Current guidelines and recommendations on this topic were initially designed for TNF inhibitors and later extrapolated to other classes of biologic agents. Thus, they should be revised to better align with the specific pathogenic mechanisms of drugs and clinical evidence, emphasizing individualized treatment approaches.

Keywords: psoriasis, biologic treatments, infections, vaccinations

Introduction

Psoriasis is a chronic inflammatory skin disease affecting between 2% and 3% of the global population.[1,2] Psoriasis is now recognized as a systemic condition.[3] Up to 30% of patients will develop psoriatic arthritis, and approximately 1% are affected by inflammatory bowel disease.[2,4] Psoriasis is also associated with multiple comorbidities such as metabolic syndrome, cardiovascular disease, and depression.[4] Additionally, psoriasis may increase cancer risk, probably due to a chronic inflammatory state with elevated levels of proinflammatory cytokines, alongside greater exposure to carcinogens.[5] Consequently, the morbidity and mortality of patients with psoriasis is increased.[2]

While the link between infections and psoriasis in patients without systemic treatment has been less explored compared to other comorbidities, there is evidence that psoriasis patients have a higher risk of infections regardless of the treatment they receive.[6]

A recent population-based study including 94,450 patients with psoriasis who were matched to 566,700 controls demonstrated a higher incidence rate (IR) (per 100,000 person-years) of severe infections requiring hospitalization (eg, respiratory, nervous system, gastrointestinal infections, among others) in patients with mild psoriasis (less likely to require systemic treatment) compared to the general population (IR 2,364.4 [95% CI 2,350.9–2,377.9] vs 2,979.1 [95% CI 2,939.0–3,018.8]).[7] The authors attributed this increased risk of infections to the altered immune environment in psoriasis patients, which involves leukocytes and proinflammatory cytokines.[7]

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Additionally, the same study reported a significantly higher IR of hepatitis B and C in patients with mild psoriasis compared to the general population (21.23 [95% CI 20.05–22.48] vs 30.28 [95% CI 26.78–34.23]).[7] A recent meta-analysis confirmed the association between psoriasis and a higher prevalence of hepatitis C virus (HCV).[8] The authors identified 389 shared genes associated with hepatitis C and psoriasis, highlighting several potential common disease targets, including interleukin (IL)-6, tumor necrosis factor (TNF), IL-10, signal transducer and activator of transcription (STAT)3, chemokine (C-X-C motif) ligand (CXCL)8, and vascular endothelial growth factor (VEGF)-A, among others.[8]

It is well established that patients receiving biologic therapy with TNF inhibitors have an increased risk of infections.[9] TNF is a proinflammatory cytokine with pleiotropic effects.[10] In the pathophysiology of psoriasis, TNF, produced by macrophages, T-lymphocytes, neutrophils, and natural killer (NK) cells, initiates a cascade of inflammatory mediators, including cytokines and chemokines, that contribute to promoting inflammation and altering cell survival and proliferation[11.] Additionally, TNF enhances keratinocyte activation and induces epidermal hyperplasia.[12] Regarding infection control, TNF plays a crucial role in granuloma formation and maintenance through monocyte and lymphocyte recruitment to the site of the infection,[10,13] contributing to the control of intracellular pathogens such as mycobacteria or fungi.[10,14] The increased risk of reactivation of latent tuberculosis with TNF inhibitors has been widely reported, especially with infliximab and adalimumab.[15] TNF also contributes to the control of other intracellular pathogens such as *Listeria monocytogenes* by promoting macrophage M1 polarization, and viruses by enhancing the apoptotic death of virus-infected cells.[10] The risk of infection in patients under treatment with TNF inhibitors can be exacerbated by other concomitant conditions such as the use of corticosteroids,[16] or the presence of comorbidities such as diabetes, common in psoriasis patients.[17]

The introduction of TNF inhibitors in the late 1990s revolutionized the management of psoriasis. However, it is now understood that psoriasis is driven by a dysregulated cytokine network, partly resulting from interactions among various subsets of T cells, such as Th17 cells and regulatory T cells.[18,19] Consequently, cytokines other than TNF, including IL-23 and IL-17, are now recognized as crucial contributors to the pathogenesis of psoriasis.[18,19]

The onset of psoriasis may involve the release of interferon (IFN)-α by plasmacytoid dendritic cells following skin injury.[20] This drives the activation of myeloid dendritic cells, which subsequently produce IL-23, a cytokine composed of the p19 and p40 subunits, the latter being shared with IL12.[21] IL-23 promotes the differentiation and expansion of Th17 cells, leading to the production of IL-17 (their characteristic) as well as other cytokines.[19] The IL-17 family of cytokines, which consists of six members (IL-17A to F) plays a key role in host defense mechanisms and inflammatory immune responses.[22] Among them, IL-17A, IL-17F, and IL17C promote inflammation through several mechanisms, including the recruitment of neutrophils, induction of antibody production, activation of keratinocytes and T cells, and stimulation of proinflammatory cytokines' production.[23] Concurrently, IL-12 drives differentiation of Th1 cells and production of IFN-γ and TNF.[24]

The improved understanding of psoriasis pathophysiology has led to development of other biologic therapies beyond TNF inhibitors, including IL-12/23 inhibitors (ustekinumab), IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, bimekizumab) and IL-23 inhibitors (tildrakizumab, guselkumab, risankizumab), which have shown excellent results in controlling the disease[25] and high probabilities of treatment persistence in the long term.[26,27] Nonetheless, due to their distinct targets, their side effects profiles, including infections, may differ substantially from that associated with TNF inhibitors.

The Summary of Product Characteristics (SmPC) and label statements regarding the management and prevention of infections or the administration of vaccines were initially designed for TNF inhibitors and subsequently extrapolated to other classes of biologic agents. This approach does not account for differences in mechanisms of action and lacks evidence addressing critical issues such as mycobacterial or viral reactivation, the risk of severe infections, spread of live vaccines, or impairment of immune responses to vaccinations, among others.

This narrative review aims to summarize the current evidence on the risk of infections in patients undergoing biologic treatment for psoriasis and provide current recommendations and practical considerations for prevention, including vaccination, screening, and management strategies.

Search Strategy

An electronic literature search was conducted on the Medline/PubMed database up to January 2025 using Medical Subject Headings (MeSH) terms and relevant medical terminology. The search criteria included the terms "psoriasis", "biologic", "infection", or "vaccination". We considered original studies, reviews, systematic reviews, meta-analyses,

letters to the editor, editorials, and experts' opinions specifically related to the topic of the review. On the other hand, congress proceedings or studies related to other specific psoriasis treatments besides biologics were excluded. Only English-language manuscripts were included. The selection of publications was conducted by two independent researchers (LM, LP), and discrepancies were resolved by consensus.

A total of 291 articles was initially identified. Duplicates and studies that did not offer pertinent information according to the research objectives were excluded. After a comprehensive review of the full-text articles, 106 studies were deemed eligible for inclusion in the review.

Infections

Tuberculosis

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium (M) tuberculosis* complex. It remains a significant global health concern and is the leading cause of death worldwide due to a single infectious agent.[28] Approximately one- quarter of the global population is estimated to have been infected with TB, and 7.5 million people were newly diagnosed globally in 2022.[29] The prevalence of latent tuberculosis infection in patients with moderate to severe psoriasis has been reported as 4.5% in the United States.[30]

TB is primarily transmitted through inhalation of droplets containing the mycobacteria.[31] Once in the alveoli, the mycobacteria are phagocytosed by macrophages or infect alveolar epithelial cells which leads to pulmonary tissue destruction.[32] *M. tuberculosis* can inhibit the lysosome-phagosome fusion, allowing intracellular replication within macrophages until cellular lysis occurs. This cycle of bacterial release and subsequent re-phagocytosis perpetuates the infection.[33] In immunocompetent hosts, lung dendritic cells migrate to draining lymph nodes, inducing a Th1 response mediated by IL-12.[33] IFN-γ-producing CD4+ T-cells are recruited to the infection site, where they secrete inflammatory cytokines such as IFN-γ and TNF. This results in macrophage activation and M1 polarization by IFN-γ, enabling the destruction of intracellular mycobacteria, while activated CD8+ T-cells lyse infected host cells; TNF amplifies the activation of macrophages and promotes their survival, recruitment and organization.[33] These processes promote the formation and maintenance of granulomas, effectively controlling the infection.[33] This leads to an asymptomatic non-contagious latent stage, known as latent tuberculosis infection (LTBI). Approximately 90% of individuals with LTBI will remain latently infected without progression to active TB, whereas the remaining 10% will develop active TB.[32] Reactivation of LTBI can occur in the context of immune suppression,[32] either due to impaired antigen presentation or interferences with Th1 responses and granuloma integrity.[33] Accordingly, TNF inhibition carries a notable risk of TB reactivation[34,35] Meta-analyses consistently demonstrate that patients with LTBI receiving TNF inhibitors for conditions such as rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis have up to a four-fold increased risk of developing active TB compared to those receiving other treatments.[34–37] The global crude rate of TB associated with TNF inhibitor therapy has been estimated at 47.6 per 100,000 persons,[35,38] with higher rates observed for infliximab and adalimumab compared to etanercept.[35,39]

Consequently, screening for LTBI and initiation of corresponding treatment to minimize the risk of reactivation according to local guidelines are recommended prior to starting TNF inhibitor therapy.[40,41] Data from a national registry prospectively following 5198 rheumatologic patients receiving biologic treatment showed that compliance with screening and treatment of LTBI produced a 10-fold decrease of the incidence of active TB in patients treated with TNF inhibitors.[42]

Although the Th17 axis appears to play a more subtle role compared to the Th1 axis, IL-17 and IL-23 are implicated in the pathophysiology of TB, especially regarding the early phases of infection.[33] IL-17 and IL-23 promote the formation of tertiary lymphoid structures (TLS) and induce the expression of CXCL13, which mediates the recruitment of TLS-associated T follicular helper cells.[33,43] TLS facilitate interactions between adaptive and innate immunity, through the interaction of Th17 axis and type 1 interferons, enhancing granuloma formation and T-cell recall responses in TB.[33] Additionally, Th17 cytokines promote the recruitment of neutrophils to the lungs, which is increasingly recognized as a relevant mechanism in the immune response to *M. tuberculosis* infection.[44]

On the other hand, emerging and growing evidence suggests LTBI reactivation rates may not be significantly affected by IL-17 or IL-23 inhibitors.[37,45–47] A cohort study involving 35 patients with psoriasis and untreated LTBI reported no cases of TB reactivation after a median of 24 months of treatment with risankizumab (21 patients), guselkumab (5 patients), tildrakizumab (5 patients), ixekizumab (2 patients), secukinumab (1 patient) and brodalumab (1 patient).[45] A multicenter retrospective study assessing LTBI reactivation risk in 405 patients with moderate-to-severe psoriasis treated with IL-23 or IL-17 inhibitors showed similar findings.[48] Of these patients, 41 received incomplete TB prophylaxis and 112 received no prophylaxis at all. Only one case of LTBI reactivation was reported after 14 months of treatment with ixekizumab.[48] The overall TB reactivation rate was 0.46% for IL-17 inhibitors and 0% for IL-23 inhibitors.[48]

Notably, in the pivotal Phase 3 clinical trials evaluating the efficacy and safety of risankizumab for moderate-to-severe psoriasis, no cases of active TB were detected among patients with LTBI, regardless of whether they received TB prophylaxis (72 patients) or not (31 patients).[49] It is worth mentioning that ustekinumab, which inhibits the p40 subunit shared by IL-12 and IL-23, may impair TB control as IL-12 plays a role in the Th1 response leading to granuloma formation.[50] Consequently, cases of TB reactivation have been reported with the use of ustekinumab.[51–53]

However, screening and treatment of LTBI remain recommended according to the SmPCs and current European guidelines prior to initiating any kind of biological treatment for psoriasis,[40,54] which may lead to a potential risk of over-screening and over-treatment.[55] To facilitate the integration of the latest evidence into clinical practice, an expert consensus on current recommendations was recently published.[41] According to this consensus, screening for LTBI or TB before initiating any biologic therapy for psoriasis is advised.[41] In many health care systems there is a strong economic incentive to start adalimumab biosimilars as biologic treatment in biologic-naive patients. In this setting, it might be reasonable to screen most patients for LTBI and make a post-hoc decision regarding inception of TB preventive therapy or choice of another biological agent not requiring TB reactivation preventive treatment. IL-17 or IL-23 inhibitors are preferred in patients with high risk of exposure to TB or of developing TB disease after infection, such as those with concomitant HIV infection, even if screening results are negative.[41] In patients with positive screening results, IL-17 and IL-23 inhibitors are also preferred when there is a high risk of anti-TB treatment toxicity or drug-drug interactions; in those cases, LTBI treatment should be waived.[41] Similarly, in psoriasis patients receiving IL-17 or IL-23 inhibitors who develop active TB disease, psoriasis treatment can be maintained alongside TB treatment. In contrast, TNF or IL-12/23 inhibitors should be discontinued and switched to IL-17 or IL-23 inhibitors once psoriasis treatment can be safely resumed.[41] Finally, periodic TB screening may only be necessary for patients receiving TNF or IL-12/23 inhibitors who are at high risk of TB exposure or progression to TB disease once infected.[41] Figure 1 illustrates the decision tree for selecting biologic treatment after LTBI screening.

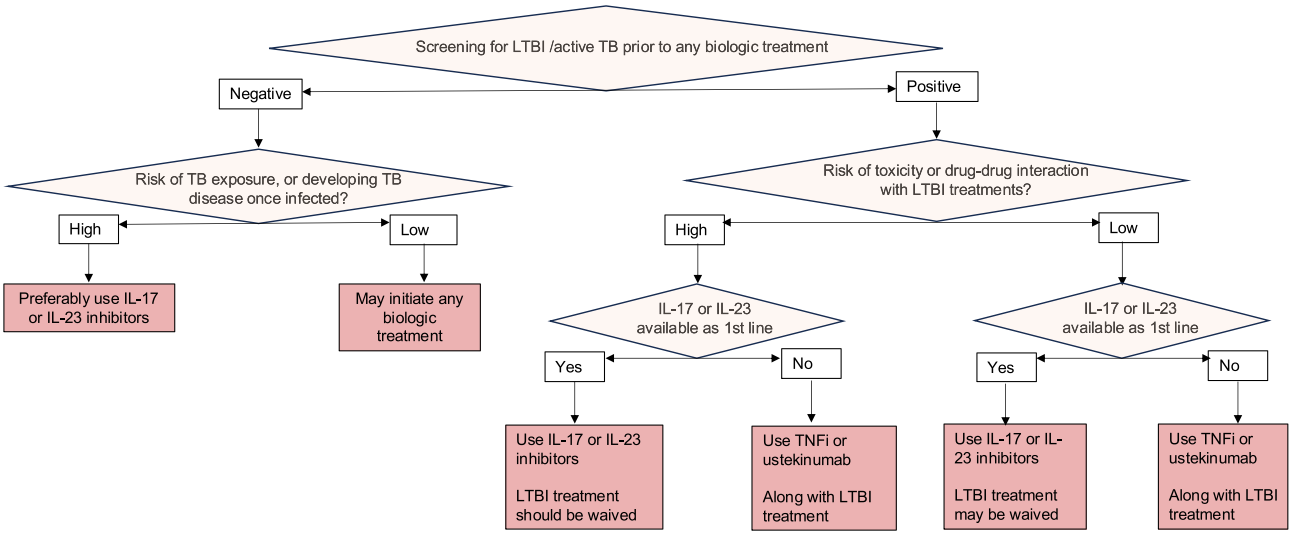

Figure 1 Decision tree for selecting biologic treatment after LTBI screening. In patients with documented active or latent tuberculosis (TB) infection, IL-17 or IL-23 inhibitors should be prioritized when available as first-line options. Otherwise, TNF inhibitors or ustekinumab should be administered along with TB treatment. When screening for TB is negative, IL-17 or IL-23 inhibitors should be preferred when the risk of TB exposure or development is high. Data from Torres et al.[41]

Hepatitis B Virus Infection

Hepatitis B virus (HBV) infection is a significant global health concern. According to data from the World Health Organization, approximately 296 million people were chronically infected worldwide in 2019[56,57], with the prevalence of infection varying across regions.[56] Chronic HBV infection significantly increases the risk of developing hepatocellular carcinoma and cirrhosis, especially when acquired during childhood.[58] HBV serologic status is commonly assessed through a triple serology panel, which includes the determination of hepatitis B surface antigen (HBsAg), antibodies to HBsAg (anti-HBs), and antibodies to hepatitis B core antigen (anti-HBc). This approach enables the differentiation of the various HBV serologic states,[59] providing valuable insights into infection status, immunity, and exposure history.

Acute HBV infection is defined serologically by the presence of HBsAg, together with anti-HBc immunoglobulin M and anti-HBc antibodies.[59] Patients with anti-HBc antibodies can be classified as having either chronic HBV infection, defined as the presence of HBsAg for 6 months or longer, or resolved HBV infection, defined as a negative HBsAg infection.[59,60] Resolved HBV infection may further reflect different scenarios: a resolved past infection, an occult HBV infection, a false-positive anti-HBc result, or a replicative HBsAg–negative infection.[60] In these cases, detecting and quantifying HBV DNA can help identify occult infections.[59,60] Even when both HBsAg and HBV DNA are undetectable, HBV infection persists due to the presence of covalently closed circular HBV DNA in hepatocytes, which can remain indefinitely and eventually lead to HBV reactivation.[59] Although not included in the routine triple serology screening for HBV, serologic clearance of hepatitis B e antigen (HBeAg) with undetectable HBV DNA, alongside HBsAg serologic clearance, serve as indicators of the host's progressive immunity against HBV infection.[61]

The clearance of HBV primarily depends on the immune system's antiviral response, initiated by the intrahepatic innate immune system. This response involves the local and systemic production of cytokines such as IL-1, IL-2, IL-4, IL-6, and IL-12, among others, which play a critical role in controlling the infection.[62] TNF, a key component of the Th1 response, plays a crucial role in the HBV-specific immune response.[63] In a study analyzing blood samples from 210 patients with chronic HBV infection and low hepatic enzymes levels, as well as 28 patients experiencing a hepatitis B flare, TNF-producing HBV-specific CD4+ T cells were identified as the dominant subset of HBV-specific CD4+ T cells. This finding suggests that these cells could play a pivotal role in the immune response against HBV.[63]

The use of TNF inhibitors has been associated with an increased risk of HBV reactivation and liver injury.[64–66] Risk factors for viral reactivation include positivity for HBsAg and hepatitis B envelope antigen (HBeAg), as well as the absence of antiviral prophylaxis.[67]

IL-12 also drives the Th1 response and plays an important role in controlling HBV infection by promoting cell-mediated immunity. It stimulates the production of IFN-γ, which inhibits HBV replication.[68] Consequently, ustekinumab carries a potential risk of HBV reactivation, with some cases documented in the literature.[59]

However, some studies suggest that the risk of HBV reactivation in patients with anti-HBc positivity but HBsAg negativity is very low.[67] In a retrospective cohort study of 8887 patients who initiated TNF inhibitors between 2001 and 2010, no cases of HBV reactivation were reported in patients with HBsAg-negative results. In contrast, the annual risk of HBV reactivation was as high as 39% in patients with HBsAg positivity.[67]

Similarly, in a retrospective study of 30 patients undergoing biologic therapy for psoriasis –26 of them seropositive for HBV (including one patient with HBsAg positivity) and 4 for HCV– no cases of hepatitis or viral reactivation were reported during a mean follow-up of 4.85 ± 3.1 years.[69] Additionally, a systematic review was conducted to evaluate the risk of HBV and HCV reactivation during biologic therapy for psoriasis (including TNF inhibitors and ustekinumab). This analysis included 312 patients with a mean follow-up of 30.9 months. Among patients with chronic HBV infection, 8 out of 40 (20%) experienced a viral reactivation, yielding a calculated yearly reactivation rate of 13.92%. Among patients with anti-HBc positivity only, 2 out of 175 (1.14%) exhibited viral reactivation, corresponding to a yearly reactivation rate of 0.32%.[69] Notably, the adjusted yearly reactivation rate for patients with chronic HBV who received antiviral prophylaxis was 7.74%, versus 26.31% for those who did not.[69]

A recent meta-analysis evaluating the reactivation rates of hepatitis B or C or HIV in patients with psoriasis receiving biological therapies (TNF inhibitors and ustekinumab) included 1033 patients and reported pooled VHB reactivation rates of 0.04 (95% CI 0.00–0.10; P< 0.001).[66] However, when stratified by region, the pooled rates differed: 0.10 (95% CI 0.03–0.19) in Asia, and 0.00 (95% CI 0.00–0.01) in Europe.[66]

The Th17 axis, involving the production of IL-17 and IL-23, has also been implicated in the host immune response against HBV infection by suppressing HBV replication.[62,70–72] Although reported HBV and HCV reactivation rates in patients treated with secukinumab have been as high as 15.2% and 7.1%, respectively,[73] in a recent multicenter retrospective cohort study involving 60 patients with psoriasis treated with secukinumab only one case of viral reactivation was reported, involving both HBV and HCV.[74] Additionally, in a phase 3 randomized placebo-controlled trial assessing the efficacy and safety of guselkumab in psoriatic arthritis only one case of hepatitis B was reported.[75] No cases of HBV reactivation have been reported with other IL-17 or IL-23 inhibitors.[40,76]

Current guidelines recommend screening for hepatitis B before initiating biological therapies for psoriasis, regardless of the drug class.[54] Screening should include serologic tests for HBsAg, anti-HBc, and anti-HBs. In cases of positive HbsAg or anti-HBc results, testing for HBV DNA is also advised.[54,77]

For inactive HBV carriers (HBsAg+, anti-HBc+, HBV DNA < 2000 IU/mL, with normal transaminase levels) undergoing high-risk biologic treatments (TNF inhibitors, ustekinumab), prophylactic antiviral treatment with lamivudine or entecavir is recommended.[59,77,78] This treatment should begin at least two weeks before starting biologic therapy and be continued for up to 6 months after its discontinuation.[59,77,78] For patients receiving other biologic treatments (IL-17 inhibitors, IL-23 inhibitors), regular monitoring for viral reactivation is advised, including determinations of serum alanine aminotransferase (ALT) and HBV DNA levels every 3 months.[59,77] The decision to prescribe prophylactic treatment for HBsAg negative and anti-HBc positive patients remains controversial.[79–82] One possible strategy is to test for HBV DNA to determine the need for prophylaxis or monitor HBsAg, ALT, and potentially HBV DNA levels during treatment. Ideally, this decision should involve consultation with a hepatologist.[54,77,83]

Finally, triple-negative serologic results for HBsAg, anti-HBc, and anti-HBs indicate a lack of immune protection, often due to the absence of prior vaccination.[59] Current guidelines recommend verifying the vaccination status of the patient and completing the vaccination schedule before starting any biologic treatment.[84] A complete vaccination series requires at least three doses administered at one-month intervals, with the first dose given at least two weeks before treatment.[59] HBV vaccination should be prioritized before starting TNF inhibitors or ustekinumab.[59,85] A prospective cohort study of 62 patients with inflammatory arthritis receiving TNF inhibitors and 38 controls found that only 20 patients (32.3%) had a positive response to HBV vaccination, compared to 36 (94.7%) of age-matched controls ($P<0.001$).[86] This finding raises concerns about whether TNF inhibitor treatment should be delayed in patients who are candidates for HBV vaccination. There is no evidence that IL-17 or IL-23 inhibitors interfere with vaccination response.[87] These agents may be preferable in such patients to avoid delaying treatment initiation. Figure 2 shows the decision flowchart based on HBV serology results.

Hepatitis C Virus Infection

Although significant global progress has been made toward the elimination of HCV infection, the World Health Organization estimated that, in 2019, 57.8 million individuals (0.8% of the global population) were living with chronic HCV infection.[88] Furthermore, approximately 20–30% of patients with chronic HCV will develop cirrhosis, and 1–4% will progress to hepatocellular carcinoma.[88]

Notably, a substantial proportion of individuals with HCV infection remains unaware of their status.[59,88] Consequently, HCV infection continues to pose a significant public health concern, and current guidelines advocate for routine HCV screening in all patients receiving biologic treatment.[54] The presence of anti-HCV antibodies serves as a diagnostic marker for HCV infection.[59] For patients with positive antibody results, testing for HCV RNA (or HCV core antigen when RNA testing is unavailable) is recommended to confirm active infection.[59]

The HCV core protein has been postulated to inhibit the TNF-mediated apoptotic signaling pathway, thereby enhancing HCV replication and allowing evasion of the host antiviral immune response.[89] Consequently, TNF inhibitors may increase viral replication and exacerbate chronic HCV infection.[59]

In a systematic review, Snast et al reported that three out of 97 hCV-infected patients experienced viral reactivation during biologic treatment (with TNF inhibitors or ustekinumab) for psoriasis, corresponding to an annual HCV reactivation rate of 2.42%.[69] Similarly, in a meta-analysis including 1033 psoriasis patients treated with TNF inhibitors or ustekinumab, Li et al documented a pooled HCV reactivation rate of 0.07 (95% CI: 0.02–0.14).[66]

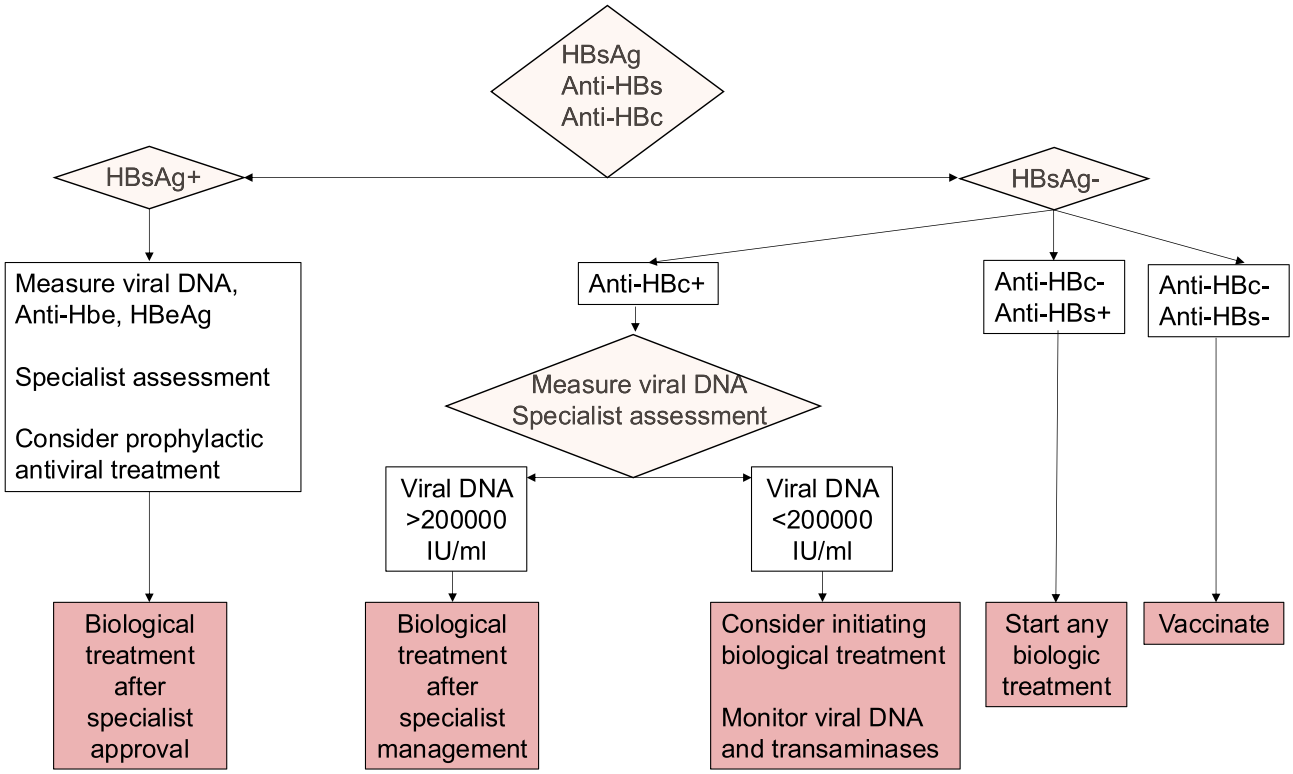

Figure 2 Decision flowchart based on HBV serology results. In cases of positivity for HBsAg or anti-HBc, specialist assessment is recommended prior to initiating biologic therapy. On the other hand, anti-HBs negativity indicates a lack of immunity and a candidate for vaccination. Data from Romiti et al.[82]

Some researchers advocate etanercept as the preferred biologic therapy for patients with HCV infection due to its relatively weaker effects on TNF activity compared to TNF inhibitors that target both soluble and cell-surface TNF.[59] Additionally, in a randomized placebo-controlled trial of patients with chronic HCV infection, those treated with etanercept in combination with standard therapy (interferon-α and ribavirin) demonstrated higher sustained virologic response rates and fewer adverse events compared to those receiving standard therapy alone.[90]

For patients with chronic HCV infection undergoing TNF inhibitor therapy, guidelines recommend liver function monitoring every three months, including HCV RNA and ALT testing.[91] Moreover, TNF inhibitor therapy is contraindicated in patients with cirrhosis, and the benefit-risk ratio must be carefully assessed on an individual basis.[91]

As with HBV infection, reports of HCV reactivation in patients treated with IL-17 or IL-23 inhibitors are anecdotal,[76,92] suggesting that these agents may be a safer alternative for HCV-infected patients. However, long-term safety data remain insufficient to draw conclusions, particularly regarding the impact of cirrhosis and potential, albeit unlikely, interactions between biologic therapies and antiviral agents.

Human Immunodeficiency Virus (HIV) Infection

Although the prevalence of psoriasis is similar in HIV-positive and HIV-negative populations,[77] psoriasis in HIV-infected patients is often severe, progressive, and refractory to first-line treatments, frequently necessitating biologic therapies.[77,93]

Evidence regarding HIV reactivation with biologic therapies remains controversial.[66,94,95] As HIV-positive patients are excluded from clinical trials, data on the optimal therapeutic management of psoriasis in this population derives solely from real-world studies. Recommendations from a panel of HIV and dermatology experts, based on a comprehensive review of existing evidence, have assessed the risks and benefits of systemic treatments for psoriasis in HIV-positive patients relative to immune system functional status.[96] They concluded that, in individuals with well-controlled HIV infection (suppressed viral load and normalized CD4 counts), biologic therapies for psoriasis do not confer an increased risk of infections compared to the general population.[96]

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While most case reports and case series regarding the safety of TNF inhibitors and ustekinumab in HIV-positive patients report favorable outcomes in terms of efficacy and safety,[93,97] with no significant changes in viral load, it is essential to consider the potential publication bias favoring successful, uncomplicated cases. A recent meta-analysis reported a pooled HIV reactivation rate of 0.12 (95% CI: 0.00–0.40) associated with TNF inhibitors and ustekinumab.[66] Furthermore, a systematic review investigating biologic therapies in psoriasis patients with HIV found a 14.4% rate of serious adverse events, primarily infections, and two (1.8%) treatment-related deaths during etanercept therapy,[93,98] although these cases did not necessarily correlate with increased viral load.[93]

Regarding IL-17 and IL-23 inhibitors, several case reports indicate that these treatments are effective and safe for managing psoriasis in HIV-positive patients, with no observed viral reactivation or serious adverse events.[99–101] Moreover, a recent systematic review suggested that risankizumab and guselkumab achieved the most favorable outcomes in terms of psoriasis clearance, making the IL-17/23 pathway a potential first-line therapeutic option for these patients.[98]

Since HIV infection may be asymptomatic, HIV screening is recommended before initiating biologic therapy.[66,84,96] For those with positive results, HIV replication should be assessed and managed by an HIV specialist before initiating biologic treatment for psoriasis.[96] In patients with uncontrolled HIV (eg, untreated or unsuppressed viral load), priority should be given to starting antiretroviral therapy and achieving viral suppression prior to initiating psoriasis treatments.[96]

Cutaneous Infections

Biologic therapies for psoriasis have been associated with bacterial, viral, and fungal cutaneous infections. A follow-up survey involving 878 patients with psoriasis receiving biologic treatments revealed that bacterial cutaneous infections, primarily cellulitis, occurred in 12 patients (1.37%).[102] Treatment with TNF inhibitors (OR 9.917, 95% CI 2.069–47.572, P = 0.004) and IL-17 inhibitors (OR 10.798, 95% CI 2.35–49.616, P = 0.002) was significantly associated with an increased risk of cutaneous bacterial infections in multivariate analysis.[102] Cutaneous viral infections were observed in 11 patients (1.25%), with herpes zoster as the most common presentation (9/11, 82%).[102] However, viral infections were not significantly associated with any specific biologic therapy in the multivariate analysis.[102] Finally, fungal infections were reported in 45 patients (5.13%), tinea (33/45, 73%) being the most common, followed by candidiasis (12/45, 27%).[102] Fungal infections were more frequently associated with IL-17 inhibitors compared to other biologics (OR 2.286, 95% CI 1.026–5.095, P = 0.0432).[102] The authors acknowledged that the low overall incidence of infections in the study could hinder the identification of other contributing factors.[102] In a meta-analysis combining data from several national registries (Italian, Spanish, and Israeli) involving 17,739 patients and 23,357.5 person-years of follow-up, the adjusted hazard ratio for bacterial cutaneous infections was 1.00 (95% CI 0.62–1.61) for patients receiving TNF inhibitors compared to those receiving non-biologic systemic therapies.[103]

IL-17 plays a critical role in the defense against extracellular pathogens, particularly fungi.[104,105] Experimental studies have shown that IL-17 deficient mice are at increased risk of systemic and mucosal candidiasis,[106] and inborn errors in the IL-17 pathway in humans are associated with chronic mucocutaneous candidiasis.[107] Accordingly, treatment with IL-17 inhibitors is associated with an increased risk of *Candida* infections.[108] However, these infections are generally not severe. An integrated safety analysis of 25 clinical studies involving 6892 psoriasis patients treated with ixekizumab demonstrated that, although the incidence of candidiasis was 4.9% (incidence rate: 1.9 per 100 person-years), they were single (non-recurrent), mild to moderate, and did not necessitate discontinuation of biologic therapy in most cases[105]. Therefore, the risk of cutaneous fungal infections should not preclude the use of IL-17 inhibitors unless an individual is at a high risk for serious cutaneous infections.

Other Infections

Intracellular and parasitic infections, such as leishmaniasis,[109,110] Chagas disease,[111] leprosy,[112,113] and strongyloidiasis,[114] have been reported to worsen or reactivate in patients undergoing TNF inhibitor therapy, particularly with monoclonal antibodies.

A recent observational cohort study involving 19,552 patients initiating TNF inhibitors (psoriasis: n = 8508, 44%; psoriatic arthritis: n = 7596, 39%; hidradenitis suppurativa: n = 3304, 17%) found an incidence rate of invasive fungal infections (IFIs) of 3.8 per 1000 person-years, indicating that fewer than 0.5% of patients developed an IFI within the first year of therapy, with no substantial variation by drug.[115] The study found that IFIs were significantly associated with

corticosteroid use (incidence rate: 2.7, 95% CI 1.5–4.7, P < 0.001) but not with the specific indication for TNF inhibitor or antifungal prophylaxis.[115] Similar findings have been reported in other studies.[16] While candidiasis was the most frequently observed TNF inhibitor-associated IFI (47% of cases), cases of histoplasmosis (12%) and coccidioidomycosis (11%) were also reported, with their incidence varying by geographic region.[115]

To mitigate these risks, appropriate screening procedures and preventive measures should be implemented prior to initiating TNF inhibitor therapy. The selection of screening tests and preventive strategies should be tailored to the individual, considering epidemiological background, geographic origin, and potential exposure to endemic diseases. This personalized approach is essential to ensure the safe use of TNF inhibitors in patients at risk for these infections.

Vaccination

Recommended Vaccines and Risk of Infection

Large population-based studies suggest that patients with psoriasis, regardless of their treatment regimen, have higher rates of serious infections requiring hospitalization compared to adults without psoriasis.[116] Among these, lower respiratory tract infections are the most common.[116]

As discussed throughout this review, the mechanisms of action of certain biologic drugs may increase the risk of infections in these patients. Some of these infections can be prevented through vaccination, which is a key measure in protecting psoriasis patients (and the general population) from infectious diseases.[116] However, vaccination rates among patients with psoriasis remain suboptimal.[116–118] A recent cross-sectional study of 5184 patients with psoriasis or psoriatic arthritis receiving biologic treatment revealed vaccination rates of only 9.14% for influenza, 7.67% for herpes zoster, and 17.64% for pneumococcal disease.[118] These rates were even lower in patients aged 19–64 years compared to those aged ≥65 years.[118] Furthermore, HBV vaccination rates were particularly low, with only 3.16% of patients who had abnormal HBV surface antigen tests receiving vaccination before starting biologic therapy.[118] A recent cohort study using a large population database found that psoriasis patients were less likely to receive influenza vaccination compared to rheumatoid arthritis patients, even when both groups were receiving systemic or biologic treatment. This discrepancy may be attributed to the younger age of psoriasis patients and insufficient counseling regarding vaccination.[116] These findings highlight the critical role of dermatologists in advising patients with psoriasis about the importance of vaccination.[116]

Current European guidelines state that psoriasis alone should not be considered a reason to deviate from standard vaccination practices. Before initiating systemic or biologic treatment, vaccination status should be reviewed and updated in accordance with national guidelines.[84] Annual inactivated influenza vaccines and up-to-date COVID-19 vaccinations are also advised.[118,119]

Since pneumococcal disease may be more severe in patients undergoing immunosuppressive treatment, local guidelines may recommend vaccination at earlier ages than in the general population.[118] However, these recommendations do not take into account the type of biological therapy being administered or its diverse immunosuppressive potential, as evidence regarding IL-17 or IL-23 inhibitors remains very limited. The same applies to the recombinant herpes zoster vaccine.[118] Patients with psoriasis have a higher risk of developing herpes zoster, especially in cases of severe psoriasis,[120] and some treatments, such as TNF inhibitors, may increase the risk of complications like postherpetic neuralgia.[121] Therefore, depending on the country and local guidelines, this vaccine may be recommended at earlier ages for patients undergoing any biological treatment for psoriasis,[118] even though patients with psoriasis treated with IL-17 and IL-23 inhibitors have a lower risk of herpes zoster and other viral diseases than those treated with TNF inhibitors.[122]

The European League Against Rheumatism advises that vaccines should be administered during periods of disease remission, ideally before starting immunosuppressive therapy.[123] The United States National Psoriasis Foundation medical board, following a literature review and Delphi process, concluded that for patients receiving non-live vaccines—which do not pose a risk of infection—biologic therapies for psoriasis or psoriatic arthritis can be continued without interruption or dosage adjustment.[124] Table 1 summarizes common vaccines and practical recommendations for patients receiving biologic treatments for psoriasis.

Live-attenuated vaccines include mumps, measles, rubella (MMR), oral poliomyelitis, oral typhoid fever, yellow fever, varicella, rotavirus, dengue, smallpox/monkeypox, chikungunya, and Zika (under development) vaccines. In general, clinical

Table 1 Common Vaccines and Practical Recommendations for Patients Receiving Biologic Treatments for Psoriasis

	Indications	**Recommendations**
Non-live vaccine		
Hepatitis B virus	Usually administered during infancy	If not immunized, administer at least 3 doses (day 0, month 1, month 6) In patients treated with TNF inhibitors or ustekinumab, prioritize vaccination before treatment initiation. If patient is already receiving biologic treatment, do not interrupt it or modify its dose
Poliomyelitis (Salk)	Usually administered during infancy	As general population. If not immunized administer 3 doses (0, 1–2 month, 6–12 months)
Haemophilus influenzae b	Usually administered during infancy	As general population. If not immunized follow local guidelines
Meningococcal disease	Usually administered during infancy	As general population. If not immunized follow local guidelines
Tetanus toxoid (diphtheria-tetanus pertussis, tetanus-diphtheria toxoid)	Usually administered during infancy	As general population. If not immunized administer 5 doses (0, 1–2 month, 6–12 months, at least 1 year after 3rd dose, at least 1 year after 4th dose).
Hepatitis A virus	Indicated in countries with moderate-higher incidence or travelers to higher incidence countries	If not immunized follow local guidelines. Do not interrupt or modificate dose of biologic treatment
Pneumococcal disease	Local guidelines may recommend vaccination at younger ages than in the general population	I If not immunized follow local guidelines. Do not interrupt or modificate dose of biologic treatment
Recombinant herpes zoster	Local guidelines may recommend vaccination at younger ages than in the general population	Follow local guidelines. Do not interrupt or modificate dose of biologic treatment
Influenza	1 dose, yearly	Do not interrupt or modificate dose of biologic treatment
Covid-19	1 dose, yearly	Do not interrupt or modificate dose of biologic treatment
Live/attenuated vaccines		
Measles, mumps and rubella virus	Usually administered during infancy	If not immunized, administer before starting biologic treatment. 2 doses with a minimum interval of 4 weeks.
Varicella virus	Usually administered during infancy	If not immunized, administer before starting biologic treatment. 2 doses with a minimum interval of 4 weeks.
Yellow fever, dengue, chikungunya, and others	Recommended / compulsory for travel to some endemic countries.	Contraindicated / Consider risk and benefits, specially in patients receiving IL-17 or IL-23 inhibitors

practice guidelines for systemic autoimmune and inflammatory diseases recommend avoiding live-attenuated vaccines in patients receiving immunosuppressive therapy, without specifying the type of treatment administered.[123,125]

European guidelines for psoriasis advise caution regarding the administration of live vaccines but do not provide further specific recommendations.[84] The United States National Psoriasis Foundation suggests discontinuing biologic therapy for 2–3 half-lives prior to administering a live vaccine and deferring the next dose until 2–4 weeks after vaccination. This guidance applies regardless of the biologic agent used, including TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, or IL-23 inhibitors.[124]

It is noteworthy that most live-attenuated vaccines, such as MMR, varicella, or oral rotavirus, are administered during infancy. Thus, immunization is generally completed before the usual age of initiation of biologic therapy for psoriasis, making live vaccination in adults and teenagers avoidable. However, live vaccine administration can pose a challenge for travelers to specific countries where immunization against certain pathogens is recommended or even mandatory, such as yellow fever in some tourist destinations.[126] A retrospective analysis of 193 immunocompromised patients (16.6% receiving immunosuppressive or biologic therapies, such as TNF inhibitors or ustekinumab) at the London Hospital for Tropical Diseases for pre-travel consultation revealed a lack of specific recommendations and guidelines tailored to their type and degree of immunosuppression.[127] Recent case reports and series suggest that certain live-attenuated vaccines may be safe for patients receiving TNF inhibitors.[126,128] Rüddel et al reported a case of a patient with ulcerative colitis treated with infliximab who received a live vaccine and experienced only mild, short-duration fever and elevated liver enzymes, with no significant complications.[126] Similarly, the yellow fever vaccine was administered safely to a patient with Crohn's disease receiving adalimumab, with no signs of infection, negative PCR results, and immunoprotective levels of antibodies against yellow fever.[129] Scheinberg et al studied 17 patients on infliximab who received revaccination against yellow fever in Brazil.[130] None of the patients experienced symptoms of yellow fever or other complications, and 15 out of 17 patients demonstrated an adequate immunological response.[130]

A systematic review on the safety of live vaccines in immunocompromised patients analyzed data from 20,556 individuals with immune-mediated inflammatory diseases on immunosuppressive medication glucocorticoids were the most common, followed by methotrexate.[128] Of these, 218 patients were on biologic monotherapy, and 39 were on combination therapy with biologics (specific biologic agents were not specified). Among the vaccines administered, 19,630 were herpes zoster, 474 mmR, 7233 yellow fever, 202 varicella, 10 oral typhoid, 5 BCG, and one each live poliomyelitis and smallpox vaccines.[128] Vaccine-strain-related infections occurred in 12 patients (0.06%), and were mild in most cases. Two fatal cases were reported: one involved a patient with rheumatoid arthritis/systemic lupus erythematosus overlap syndrome who started methotrexate and dexamethasone treatment four days after receiving the yellow fever vaccine. This patient developed yellow fever vaccine-associated viscerotropic disease and died.[128] The vaccine batch used was associated with a 20-fold increased risk of complications.[128] The second case involved an infant whose mother was on infliximab during pregnancy. The infant received the BCG vaccine at three months of age and developed disseminated BCG infection, which was fatal.[128]

Upon reviewing the literature, it becomes evident that all biologic therapies are often grouped together when developing recommendations, without considering their distinct mechanisms of action. Most vaccination guidelines for patients on biologics are based on evidence from TNF inhibitors, that has been extrapolated to IL-17 and IL-23 inhibitors, relying on conservative expert opinion due to lack of clinical data. It is important to highlight that not all therapeutic monoclonal antibodies or biologic agents result in immunosuppression. Therefore, the specific characteristics of each agent should be evaluated before determining whether live vaccines can be administered.

Vaccine Effectiveness and Immunogenicity and Biologic Therapies

An additional concern is whether biologic treatments may diminish the immunogenic efficacy of vaccines. While humoral immunity is crucial for vaccine responses, B-cell activation and antibody production often require T follicular helper cells for T-cell dependent B-cell responses.[87] However, non-protein antigens, such as pure polysaccharide vaccines, can activate B cells independently of T cells, leading to a T-independent response. This response is generally short-lived and produces low-affinity IgM antibodies.[87]

It is plausible that treatments targeting cellular immunity may impair vaccine responses. Vaccine-induced immunity is typically measured by antigen-specific antibody levels in plasma, whereas cellular immunity assessments rely on detecting antigen-specific CD4+ and CD8+ T cells, as well as their cytokine profiles, following in vitro stimulation.[87]

The effect of TNF inhibitors on responses to inactivated vaccines is controversial.[131] Some studies have reported lower antibody levels after influenza vaccination in patients with spondyloarthritis treated with TNF inhibitors than in healthy controls (51.6% vs 74.3%, P = 0.002)[132]. TNF inhibitors have also been associated with reduced responses to HBV vaccination.[86,133] However, several randomized clinical trials have found no significant differences in immunity between patients on TNF inhibitors and controls following influenza vaccination.[119] Despite these mixed results, there is a consensus that, while immune responses may be reduced in patients receiving TNF inhibitors, protective immunity is usually achieved.[131]

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IL-12/23 and IL-17 inhibitors, in contrast, do not appear to impair vaccine responses.[87] For instance, secukinumab does not reduce humoral responses to influenza[134] or meningococcal vaccines,[131] and similar findings have been reported for ixekizumab regarding tetanus and pneumococcal vaccines.[131] Ustekinumab has not been shown to have any adverse impact on the immunogenicity of influenza, pneumococcal, or tetanus vaccines.[131] Although no data are available for guselkumab, risankizumab, or tildrakizumab, similar results can be anticipated.[131] For all classes of biologics, it has been proposed to administer vaccines mid-cycle or two weeks before the next dose to optimize vaccine responses.[131]

The immunogenicity of COVID-19 vaccines in patients undergoing biologic treatment has been extensively studied. A longitudinal cohort study involving 67 psoriasis patients receiving systemic treatment, including methotrexate (n = 14), TNF inhibitors (n = 19), IL-17 inhibitors (n = 14), and IL-23 inhibitors (n = 20), and a control group of 15 healthy volunteers was conducted.[135] A lower proportion of patients receiving methotrexate (61.5%) exhibited detectable T-cell responses (evidenced by the production of interferon-γ, IL-2, or IL-21) compared with those receiving targeted biologics (74%, P = 0.38) and healthy controls (100%, P = 0.022).[135] However, all participants demonstrated detectable neutralizing antibodies after the second vaccine dose, with similar antibody titers observed across treatment groups and healthy controls.[135] Favaro et al recently tested humoral and cellular immunity after COVID-19 vaccination in psoriasis patients treated with IL-23 or IL-12/23 inhibitors (n=21), IL-17 inhibitors (n=17), TNF inhibitors (n=20), methotrexate (n=2), and apremilast (n=3), as well as in 14 untreated patients.[136] They found that TNF inhibitors decreased antibody titers against the S1 antigen following COVID-19 vaccination, while patients treated with IL-23 inhibitors exhibited higher antibody levels, likely due to an enhancing effect on the humoral response via T-helper cells.[136] They also observed that the levels of activated CD4+ or CD8+ SARS-CoV-2-specific T cells in psoriasis patients treated with biologics were comparable to those in untreated patients or healthy donors and remained stable for months after SARS-CoV-2 infection, suggesting that a long-lasting pool of memory T cells remains present in patients treated with biologics.[136] Additionally, a meta-analysis on the immunogenicity, effectiveness, and safety of COVID-19 vaccines in patients with immune-mediated dermatological diseases reported that neither the presence of psoriasis nor the use of biologic drugs was associated with significant differences in serum anti-SARS-CoV-2 IgG antibody levels.[137]

Vaccine-Associated Psoriasis Flare-Ups

The potential exacerbation of psoriasis following vaccination may be a cause of some concern. Although establishing a direct and causal relationship between vaccination and disease flare-ups is challenging,[138] case reports have described worsening of psoriasis after certain vaccinations.[139] In fact, the term “psoriasis vaccinalis” has been suggested for vaccine-induced new-onset psoriasis.[140] New-onset or flare-ups of psoriasis have been reported following administration of several vaccines, including yellow fever, tetanus-diphtheria, BCG, pneumococcal polysaccharide, and influenza vaccines.[140] A variety of clinical presentations of psoriasis has been reported.[140] This phenomenon is particularly evident in COVID-19 vaccines,[141,142] which have been linked to cases of erythroderma[139] and generalized pustular psoriasis.[143,144] The immunologic reaction to vaccine adjuvants and immune system dysregulation due to viral components could be a potential pathophysiological mechanism.[140] Innate immunity stimulation driven by vaccination might lead to increased levels of type I interferon, promoting autoimmunity.[145–147] Vaccines without adjuvants appear to carry a lower risk of undesirable immune modulation.[148] The impact of biologic treatment for psoriasis in this setting remains unclear. Psoriasis flare-ups after vaccination have been described in patients treated with TNF inhibitors,[149] ustekinumab,[150] IL-17 inhibitors,[150] and IL-23 inhibitors.[141] Due to the role of IL-1 in pustular psoriasis and the post COVID19-vaccination inflammation, anakinra has been tested to treat these cases of flare-ups with promising results.[151]

Conclusions

This review highlights key considerations for biologic treatment in psoriasis patients, particularly regarding infection risks. It is essential to emphasize that not all psoriasis treatments have an immunosuppressive effect. While TNF inhibitors and ustekinumab are associated with an increased risk of latent tuberculosis and hepatitis B virus reactivation, biologics differ significantly in their mechanisms of action, and IL-17 and IL-23 inhibitors do not carry a significant risk of infection. Thus, institutional protocols may provide general guidance, but physicians must adapt recommendations based on the underlying pathophysiology and available evidence, while taking into consideration the country-specific

epidemiological data. Individualization of treatment remains critical. Pre-treatment screening for infectious diseases at risk of reactivation is recommended for all patients initiating biologic therapy. However, decisions regarding treatment and vaccination must consider the specific biologic agent selected.

Psoriasis patients on biologic treatment should follow the same vaccination schedule as the general population according to age. In addition, annual influenza and COVID-19 vaccines are recommended. Generally, live-attenuated vaccines should be avoided, especially during TNF inhibitor therapy. Risk-benefit assessments should be tailored to each individual, as live vaccines might be safely administered in certain cases, particularly for patients undergoing treatment with IL-17 or IL-23 inhibitors. Additionally, it is crucial to stay informed about advancements in the development of newer, more effective, and safer vaccines, as well as the growing evidence supporting the safety of biological treatments for psoriasis in patients receiving vaccinations. Furthermore, ensuring that reviews remain updated with the latest evidence is just as crucial as continuing to generate new research in this field. Particularly, prospective studies assessing the actual risk of latent infection reactivation and the safety of live vaccines in patients receiving IL-17 or IL-23 inhibitors are needed. Such evidence will help refine recommendations, ensuring they are based on robust scientific data.

Disclosure

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