Novel biologic therapies have revolutionized the treatment of psoriasis and atopic dermatitis. Although they are generally safe, they are immunomodulatory and therefore unique considerations apply in regards to infections and vaccine administration. This review aims to provide a clear and practical guide for dermatologists or other healthcare providers to reference when caring for psoriasis or atopic dermatitis patients being treated with biologic therapies using currently available guidelines and clinical data. Vaccinations for approved biologics including TNFα, IL-12/23, IL-23, IL-17, and IL-4/13 inhibitors will be discussed, with a special note on current COVID-19 vaccination recommendations.

INTRODUCTION

The development of novel biologic therapies has revolutionized the treatment of inflammatory skin conditions such as psoriasis and atopic dermatitis (AD), and in recent years these therapies have widely emerged as the preferred treatment option for patients with moderate-to-severe disease [1-5]. Biologic therapies target specific cytokines, receptors, or other cellular pathways known to play a role in the pathogenesis of these diseases, allowing targeted and directed therapy with generally fewer systemic adverse effects when compared to other systemic immunomodulatory agents [1,5]. The most effective biologics for plaque psoriasis, interleukin-23 (IL-23) and IL-17 inhibitors, have been shown to achieve a 75% or greater reduction in Psoriasis Area and Severity Index (PASI) scores in nearly 90% of patients [2]. Similarly for AD, the IL-4/IL-13 inhibitor dupilumab has been shown to achieve a 75% or greater reduction in Eczema Area and Severity Index (EASI) scores in >50% of patients [5].

Undoubtedly, the emergence of these therapies has been life changing for many psoriasis and AD patients, and the usage of biologics will likely continue to rise exponentially. Although biologic therapies are generally well-tolerated, patients receiving therapy may have increased risk of contracting certain infections and decreased capacity to respond to infections by nature of their inherent immunomodulatory and/or immunosuppressive effects [6,7].
example, tumor necrosis factor α (TNFα) inhibitors have been associated with increased rates of upper respiratory tract infections, pharyngitis, sinusitis, rhinitis, as well as reactivation of tuberculosis [8]. IL-23 inhibitors have also been associated with higher rates of upper respiratory tract infections and pharyngitis, while IL-17 inhibitors increase the risk of Candida infection [8]. Patients on the IL-4/IL-13 inhibitor dupilumab may have higher risk of herpes simplex virus infection or viral reactivation [9].

The effect each therapy has on the immune system and the degree to which each suppresses the immune response varies, and special considerations may be required for certain patients before initiation of therapy. In particular, the immunomodulatory effects of biologics may affect response to vaccinations, necessitating adjustments to normal vaccination schedules [10]. While vaccines are generally well-tolerated with very few side effects, rare immunological reactions have been reported including hypersensitivity reactions, serum sickness, Guillain-Barré syndrome, disseminated infections, and various skin manifestations such as erythema multiforme, erythema nodosum, granuloma annulare, bullous pemphigoid, Sweet’s syndrome, Gianotti-Crosti syndrome, and cutaneous lupus [11]. The true risk of these rare reactions in patients on biologics remains unknown. However, certain live-attenuated vaccines may increase the risk of disseminated infections when administered to immunocompromised patients, including patients on immunomodulatory therapies such as biologics [10].

As the primary prescribers of biologic therapies for psoriasis and AD patients, dermatologists have the crucial responsibility to understand the most up-to-date vaccination recommendations for currently available biologics. In this review, we aim to provide a clear and practical guide for dermatologists or other healthcare providers to reference when approaching vaccination for psoriasis and AD patients starting biologic therapy using currently established recommendations.

**VACCINATION SCHEDULES**

The US Centers for Disease Control and Prevention (CDC) provides free and accessible guidelines to current adult vaccination schedules online ([https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf](https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf)). The CDC Advisory Committee on Immunization Practices (ACIP) also publishes separate best practice guidelines for immunization of individuals with altered immunocompetence, including for patients on medications with immunosuppressive or immunomodulatory effects such as biologics ([https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.pdf](https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.pdf)).

**INACTIVATED VACCINES**

Inactivated vaccines include the *Haemophilus influenzae* type b, hepatitis A and B, human papillomavirus (HPV), inactivated influenza, meningococcal, pneumococcal 13- and 23-valent (PCV13 and PPSV23), tetanus and diphtheria toxoids and acellular pertussis (TDAP), and recombinant zoster vaccines (RZV) [12]. Inactivated vaccines carry no risk of causing infection, as they are composed of inactivated or killed viruses or bacteria, portions of these microbes, or toxoids [10]. All inactivated vaccines can be administered safely to patients with altered immunocompetence, though efficacy of these vaccines may vary [13]. The CDC recommends that patients age ≥19 on or initiating biologic therapy should receive the pneumococcal and annual inactivated influenza vaccinations [10,13]. Additionally, the ACIP unanimously approved new recommendations in October 2021 for all adults age ≥19 immunodeficient or immunosuppressed due to therapy to receive two doses of the recombinant zoster vaccine [14]. This differs from 2019 recommendations from the National Psoriasis Foundation suggesting that all patients with psoriasis and psoriatic arthritis >50-year-old and those <50-year-old on tofacitinib, combination immunosuppressive therapy, or systemic corticosteroids receive recombinant zoster vaccination [15].

**LIVE-ATTENUATED VACCINES**

Live-attenuated vaccines include the mumps, measles, rubella (MMR), oral poliomyelitis, oral typhoid fever, yellow fever, and varicella zoster vaccines [12,13]. Severe complications including reactivation of viruses or bacteria in live-attenuated vaccines has been documented in immunocompromised patients [13]. Although there is a lack of data on the true risk of pathogen reactivation in patients on biologic immunomodulatory therapy, current guidelines state that all live-attenuated vaccines are strictly contraindicated in these patients due to this potential risk [10,13]. If a live-attenuated vaccine is indicated due to lack of prior vaccination or no evidence of immunity, it should generally be administered 14-30 days prior to initiation of therapy or at least 3 months after cessation of therapy [16].

**COVID-19 VACCINES**

With the constantly evolving recommendations concerning vaccinations against SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), a special note must be made for vaccine administration in psoriasis and AD patients on biologic therapy. All three COVID-19 vaccines currently approved in the US (Pfizer-BioNTech BNT162b2, Moderna mRNA-1273, Johnson & Johnson’s
Janssen JNJ-78436735) are considered safe and effective in all adults, including those on biologic therapy, for preventing infection by SARS-CoV-2 [17]. On November 17, 2021, the US CDC ACIP expanded the eligibility for a third COVID-19 mRNA vaccine booster dose to all adults ages 18 and older, 6 months after receiving the second dose of either the Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273 vaccines [18]. All adults over the age of 18 who have received a single dose of the Johnson & Johnson’s Janssen JNJ-78436735 vaccine are eligible for a booster dose 2 months after their initial dose [19].

As of February 17, 2022, the CDC has released specific COVID-19 vaccination recommendations for moderately or severely immunocompromised individuals [20]. This group includes patients on TNFα inhibitors or any biologic agents that are considered immunosuppressive or immunomodulatory such as IL-17, IL-12/23, IL-23, IL-4/13 inhibitors [17,20]. For these individuals who received an mRNA COVID-19 vaccine, the CDC recommends a third dose of mRNA COVID-19 vaccine (Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273) >28 days after the completion of their second dose, followed by an additional booster dose at least 3 months after the administration of the third dose [20]. Individuals on biologic therapy who received the Johnson & Johnson’s Janssen JNJ-78436735 vaccine should receive a second dose of an mRNA COVID-19 vaccine (Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273) >28 days after the first dose, followed by an additional booster with an mRNA COVID-19 vaccine at least 2 months following the second dose [20]. Biologic medications can and should be continued during and after administration of the vaccines [17].

The rationale behind the importance of booster doses in patients receiving biologic therapy is based on preliminary data that individuals on certain immunosuppressive or immunomodulatory medications may mount an inadequate immune response to only 2 doses of mRNA COVID-19 vaccines [17]. For example, there have been clinical studies showing similar antibody titers but lower T-cell response in patients receiving TNFα, IL-23, or IL-23 inhibitors [21,22]. Additionally, the longevity of effective antibody response in patients receiving such therapies is currently unknown [22]. Clinical studies in non-immunosuppressed individuals have shown a significant increase in neutralizing antibody titers and a decrease in severe outcomes such as hospitalization or death after a third dose of the Pfizer-BioNTech vaccine without evidence of serious adverse events [23,24].

**TUMOR NECROSIS FACTOR-α INHIBITORS**

TNFα inhibitors, including infliximab, adalimumab, etanercept, and certolizumab, are biologic medications approved for the treatment of psoriasis and psoriatic arthritis [25]. Compared to other newer biologic medications, TNFα inhibitors benefit from a relative abundance of clinical studies assessing their safety and efficacy in the setting of vaccination. Numerous randomized clinical trials comparing response to influenza vaccination in patients on various TNFα inhibitors to controls have shown no difference in effective immunity [26-30]. Similarly, other clinical trials have demonstrated that TNFα inhibitors do not impact immune responses to pneumococcal vaccinations [29-32]. Live-attenuated vaccinations should be avoided in patients on all biologics.

Although biologic monotherapy is indicated for most patients and biologic medications are not frequently used concurrently, they are occasionally used together and are also sometimes used in combination therapy with other immunomodulatory agents such as methotrexate and cyclosporine [33]. Patients on TNFα inhibitor combination therapy have the same vaccination recommendations as patients on TNFα inhibitor monotherapy.

**INTERLEUKIN-12/23 INHIBITOR**

Ustekinumab, a monoclonal antibody IL-12/23 inhibitor, is approved for the treatment of psoriasis and psoriatic arthritis [1]. Live-attenuated vaccinations are contraindicated due to lack of any clinical studies assessing safety, though several studies have shown that inactivated vaccines are safe and effective. As part of a phase 3 placebo-controlled study comparing 60 psoriasis patients on long-term (≥3 years) treatment with ustekinumab compared to controls, immune response to pneumococcal (T-cell independent) and tetanus toxoid (T-cell dependent) vaccinations were assessed [34]. No differences in antibody levels were observed in the ustekinumab group compared to controls. In another prospective study looking at the effectiveness of influenza vaccination in 15 Crohn’s disease patients receiving ustekinumab, antibody titer levels and cellular immune response, measured through T-cell proliferation, was actually higher in the ustekinumab group when compared to controls [35].

**INTERLEUKIN-23 INHIBITORS**

Risankizumab, guselkumab, and tildrakizumab are monoclonal antibodies against IL-23 and have been approved for treatment of psoriasis, as well as psoriatic arthritis in the case of guselkumab [1]. There have been no clinical studies conducted evaluating the safety and efficacy of vaccinations for IL-23 inhibitors, though as with other biologics, live-attenuated vaccinations should not be administered. Inactivated vaccinations are considered safe and may still be administered, though further studies are needed to understand if therapy has any effect on their
immunogenicity.

**INTERLEUKIN-17 INHIBITORS**

Secukinumab and ixekizumab are monoclonal antibodies that inhibit IL-17A approved for treatment of psoriasis and psoriatic arthritis, while brodalumab is a monoclonal antibody targeting the IL-17 receptor alpha subunit approved for treatment of psoriasis [1]. Live-attenuated vaccinations should not be administered for any patients on anti-IL-17 therapies.

Secukinumab has been evaluated for its effect on response to influenza and meningococcal vaccinations. In one study comparing 17 patients with psoriatic arthritis or ankylosing spondylitis on secukinumab to healthy controls, secukinumab had no effect on seroconversion rates with similar increases in antibody titers 4 weeks after administration compared to the controls [36]. In another randomized, open-label, parallel-group, single-center study of 50 healthy subjects, influenza and meningococcal group C vaccinations were administered 2 weeks after receiving a single 150-mg dose of secukinumab and compared to controls who received no treatment [37]. Subsequent antibody levels to both vaccines were similar and considered adequately protective for both the secukinumab and control group.

Similarly, ixekizumab has been evaluated for its effect on response to tetanus and pneumococcal vaccinations. In a randomized, open-label, parallel-group study, 83 healthy adult subjects were given either vaccinations alone or 2 weeks after a 160-mg dose of ixekizumab with another 80-mg dose given with vaccination administration [38]. After 4 weeks, there was no difference in production of anti-tetanus or anti-pneumococcal antibodies for the ixekizumab group versus control, showing that ixekizumab had no effect on humoral immune response to these inactivated vaccines.

There are currently no clinical studies assessing the effect of brodalumab on vaccinations. Inactivated vaccinations should still be administered as recommended for patients on brodalumab, though further studies are needed to ensure there is no effect on immune response to such vaccines.

**INTERLEUKIN-4 RECEPTOR α/IL-4/IL-13 INHIBITORS**

Dupilumab, a human monoclonal antibody against IL-4 receptor α, which inhibits downstream signaling of IL-4 and IL-13, and tralokinumab, a human monoclonal antibody against IL-13, have been approved for the treatment of moderate-to-severe AD [5,39]. As with other biologic therapies, studies on vaccine efficacy and safety are limited.

In one randomized, double-blinded placebo-controlled study looking at 178 adults with moderate-to-severe AD, humoral immune response to meningococcal and tetanus vaccines were assessed after receiving 12 weeks of dupilumab [40]. Similarly, high levels of IgG antibody titers were detected in the dupilumab and placebo groups for both vaccinations with no effect on dupilumab safety or efficacy. Interestingly, the dupilumab group had significantly lower levels of vaccine-specific IgE, which may be beneficial for patients with AD by limiting the risk of adverse events during subsequent vaccination or antigen exposure. These findings concluded that inactivated vaccines are safe and immunogenic for use in patients with AD receiving dupilumab.

Similarly, a randomized, double-blinded placebo-controlled study was conducted on 215 AD patients receiving tralokinumab or placebo over 30 weeks who received the Tdap and meningococcal vaccines at week 12 [41]. At 16 weeks following vaccination, IgG levels for both vaccines and rates of adverse effects were similar between the treatment and control groups, demonstrating that treatment with tralokinumab had no effect on immune response to these vaccines.

As with other biologics, live-attenuated vaccines should be avoided after initiation of dupilumab or tralokinumab therapy.

**CONCLUSIONS**

The advent of biologic therapies has transformed the treatment of chronic inflammatory skin diseases such as psoriasis and AD, bringing safe and effective therapy to millions of patients. With the increasing use of these immunomodulatory medications, it is vital for healthcare providers and particularly dermatologists, who are the primary prescribers of biologic therapy for psoriasis and AD, to understand how to properly navigate the complex recommendations for vaccinations for these patients. As summarized in Table 1, inactivated vaccines have been proven or are assumed to be safe and effective for all patients in biologics, while all live-attenuated vaccines should be avoided. Current COVID-19 vaccination recommendations as of March 2022 are also discussed, though these remain fluid and may change as additional evidence is collected. Further investigation is also warranted for certain biologic medications for which clinical studies on vaccine safety and efficacy have yet to be formally conducted.

This review provides a concise and practical guide for vaccinating psoriasis and AD patients currently on or considering initiation of biologic therapy, using current up-to-date guidelines by the CDC and available evidence from the literature for each biologic currently approved for treatment of psoriasis or AD by the US Food and Drug
Table 1. Current Vaccination Recommendations for Psoriasis and Atopic Dermatitis Patients on Biologic Therapy

| Vaccine               | TNFα | IL-12/23 | IL-23 | IL-17 | IL-4/IL-13 | Comments                                                                 |
|-----------------------|------|----------|-------|-------|------------|-------------------------------------------------------------------------|
| Pneumococcal          | ✓a   | ✓        | ✓     | ✓     | ✓          | Should be administered to all patients age ≥19 on biologics             |
| Inactivated Influenza | ✓    | ✓        | ✓     | ✓     | ✓          | Should be administered annually to all patients on biologics            |
| Recombinant Zoster    | ✓    | ✓        | ✓     | ✓     | ✓          | Should be administered (2-doses) to all patients age ≥19 on biologicsc   |
| Other inactivated     | ✓    | ✓        | ✓     | ✓     | ✓          | Includes Haemophilus influenzae type b, hepatitis A and B, human papillomavirus (HPV), tetanus and diphtheria toxoids and acellular pertussis (TDAP) |
| Live-attenuated       | Xb   | X        | X     | X     | X          | Includes mumps, measles, rubella (MMR), oral poliomyelitis, oral typhoid fever, yellow fever, and varicella zoster                  |
| COVID-19              | ✓    | ✓        | ✓     | ✓     | ✓          | Approved for 3-dose Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273 vaccines or 1st-dose Johnson & Johnson's Janssen JNJ-78436735 + 2nd dose mRNA COVID-19 vaccine |
| COVID-19 Booster      | ✓    | ✓        | ✓     | ✓     | ✓          | Should administer additional booster of Pfizer-BioNTech or Moderna at least 3 months after 3rd dose or 2 months after 2nd dose for those who received the Johnson & Johnson's Janssen JNJ-78436735 vaccine. |

*a ✓ = Indicated for administration. bX = Not indicated for administration while concurrently on therapy. If indicated, can be administered 14-30 days prior to initiation of therapy or at least 3 months after cessation of therapy. cBased on most recent ACIP recommendations. National Psoriasis Foundation guidelines from 2019 recommend recombinant zoster vaccination for all psoriasis patients >50 and those <50 on biologic therapy only in combination with other systemic treatment.
Administration.

**Funding Sources:** This article has no funding source.

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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