Vaccine considerations for adult dermatology patients on immunosuppressive and immunomodulatory therapies: a clinical review

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Abstract

Adults with chronic inflammatory skin disease are at increased risk of vaccine-preventable illnesses and infections, likely because of the underlying disease itself and also their treatment with immunosuppressive and immunomodulatory medications. Despite the association between these agents and increased susceptibility to infection, vaccination rates in dermatology patients remain low. Although preventative care such as vaccinations is typically managed by primary care providers, dermatologists serve a critical role in spreading awareness of the specific risks of immunosuppressive and immunomodulatory agents and promoting understanding of individualized vaccine recommendations. In this review, we provide evidence-based information on vaccine recommendations for adult dermatology patients, specific to age and medication use.

Keywords: general dermatology, immunosuppression, medical, preventative care, vaccination, vaccine

Introduction

Systemic immunosuppressive and immunomodulatory medications are increasingly prescribed by dermatologists to patients with chronic autoimmune and autoinflammatory diseases. Immunomodulatory drugs are typically defined as therapeutics with effects targeting a specific pathway or cell type, whereas immunosuppressants tend to be small molecule therapeutics with broader effects on intracellular immune pathways [1]. Despite the association between these agents and increased susceptibility to infection, adherence to vaccinations in the adult dermatology population is poor [2].

Because preventative care is typically managed by primary care physicians, vaccination counseling may not be a part of standard dermatology care. Although the Centers for Disease Control and Prevention (CDC) has clear, age-specific recommendations for the general population, the application of these guidelines to dermatology patients and therapies is not clear and has been identified as a practice gap in dermatology [3]. As vaccine hesitancy, identified by the World Health Organization as a top ten threat to global health in 2019 [4], continues to grow, all physicians, including dermatologists, must play an active role in advocating for public health through regularly recommending and/or offering appropriate vaccinations.

Through educating patients on the increased risk of vaccine-preventable illnesses associated with specific immunosuppressive and immunomodulatory therapies, discussing vaccination as a routine part of care, and providing

pertinent data regarding safety and efficacy, dermatologists can significantly contribute to improved vaccine coverage and help to decrease vaccine-preventable infections. The objective of this article is to review the specific infection risks associated with dermatologic systemic therapies and vaccine recommendations for patients with chronic skin diseases on immunosuppressive or immunomodulatory therapies.

Discussion

General recommendations

Prior to starting any immunosuppressive or immunomodulatory medication, a vaccine history should be obtained and patients should be recommended to receive any necessary age-appropriate vaccinations (Table 1) and the seasonal influenza vaccine, if available. The National Psoriasis Foundation (NPF), [5] and American College of Rheumatology (ACR), [6] recommend pneumonia vaccination pneumococcal conjugate (PCV13) followed by a dose of pneumococcal polysaccharide (PPSV23) at least 8 weeks later in all patients on biologic or immunosuppressive medications, following the CDC guidelines for patients on iatrogenic immunosuppression [7]. Additionally, the hepatitis B virus (HBV) vaccine should be recommended for those desiring vaccination who do not demonstrate appropriate immunity, particularly in at-risk individuals. For vaccines given as a series (Shingrix, HBV), the first dose should ideally be given before starting therapy to ensure the best response, unless this would cause a significant delay in the start of a necessary treatment. All non-live vaccinations recommended prior to treatment can be given safely during therapy if necessary. Finally, no live vaccines should be given while on immunomodulatory or immunosuppressive therapy and instead delayed until one month or longer after discontinuation, depending on the medication and its half-life [8].

Recommendations for additional vaccinations, outside of the CDC age-appropriate recommendations, are based on an increased risk of infection associated with specific medications and the limited safety and efficacy information available in patients vaccinated while on immunosuppressive and immunomodulatory therapies. A summary of these recommendations is provided in **Table 2**. Given limited data is available examining true protection against infection, especially among dermatology patients, the immune response or antibody titers often serve as a surrogate [9].

Table 2. *Summary of drug-specific vaccine recommendations for dermatology patients, by therapy.*

Drug	Recommended Vaccines	Additional Considerations	Notes
High-dose[1] glucocorticoids	Influenza Pneumonia[2] Shingrix (≥50 years)	Shingrix in patients <50 years	Consider additional vaccinations for future steroid sparing agents
Methotrexate	Influenza Pneumonia (>65 years) Shingrix (≥50 years)		Additional vaccines may be necessary for combination therapy or those receiving >0.4 mg/kg/week
Cyclosporine, Mycophenolate, & Azathioprine	Influenza Pneumonia[2] Shingrix (≥50 years)	HPV prior to MMF	Consider additional vaccinations for CSA patients transitioning to other agents
TNF inhibitors & other biologics	Influenza Pneumonia[2] Shingrix (≥50 years)		
JAK Inhibitors	Influenza Pneumonia[2] Shingrix (≥50 years)	Shingrix in patients <50 years	
Rituximab	Influenza Pneumonia[2] Shingrix (≥50 years)		Administer vaccines 4 weeks prior to starting or at least 6 months after therapy for the best response

[1]High-dose glucocorticoids: ≥20 mg/day of prednisone for ≥2 weeks. [2]Pneumonia vaccination strategy in patients who are iatrogenically immunosuppressed: PCV13 followed by a dose of PPSV23 at least 8 weeks later.

Although vaccine immunogenicity is certainly not synonymous with efficacy, antibody level measurements following vaccination can be used as sufficient predictors of protection when true correlates of protection are difficult to measure or unknown [9].

High-dose glucocorticoids

Risk of infection

The Infectious Diseases Society of America (IDSA) guidelines define high-dose glucocorticoid therapy as ≥20mg/day of prednisone for ≥2 weeks [10]. High-dose glucocorticoids have been associated with an increased risk of infection compared to placebo in systemic lupus erythematosus (SLE) patients [11]. Although specific dosages were not taken into account, Schneeweiss et al. found that atopic dermatitis (AD) patients on prednisone had almost twice the 6-month infection risk compared to those on methotrexate (MTX), (relative risk [RR]: 1.89, 95% confidence interval [CI]: 1.05-3.42), [12]. An increased risk of herpes zoster (HZ) has been identified in patients with psoriasis, SLE, and autoimmune bullous diseases on high-dose glucocorticoid therapy [13]. Even low-dose glucocorticoids, starting at 5mg or less per day, may confer an increased risk of serious infection in patients with rheumatoid arthritis (RA), [14].

Vaccine recommendations and safety

Given corticosteroids are often used as a temporary therapy or as a bridge to longer term immunosuppressive therapy, it is critical to consider and potentially administer required vaccinations for both the corticosteroid and future therapies. An annual influenza vaccination should be administered prior to starting corticosteroid therapy, as seroconversion following influenza vaccination was reduced in SLE patients on >20mg/day prednisone [15]. Shingrix can also be considered in adults <50 years old on systemic corticosteroids due to the increased risk of HZ [13].

Methotrexate

Risk of infection

Methotrexate <0.4mg/kg/week is considered low-level immunosuppression in the IDSA guidelines [10]. Reports of an increased risk of infection in patients on MTX are contradictory and the risk may be disease specific. A randomized controlled trial investigating adverse event rates in patients with cardiovascular disease, diabetes, or metabolic syndrome on MTX (≤20mg/week) versus placebo found a small but significant increased risk of any infectious adverse event in the MTX group (hazard ratio [HR]: 1.15, 95% CI: 1.01-1.30), [16]. Conversely, an increased risk of respiratory infections was not observed in a meta-analysis examining patients with psoriasis, psoriatic arthritis, or inflammatory bowel disease (IBD) on MTX [17]. Evidence regarding the association between HZ and MTX is conflicting, as a systematic review of rheumatoid arthritis (RA) patients found that comorbidities and concurrent therapies were often confounders in studies that did suggest an increased risk of HZ [18]. Among psoriasis patients, an increased risk of HZ was observed in patients taking MTX with a concomitant biologic therapy (rate ratio [RR]: 1.66, 95% CI: 1.08-2.57) but not in those on MTX monotherapy [19].

Vaccine recommendations and safety

If available, an annual inactivated influenza vaccination should be given prior to starting MTX as MTX has been associated with a decreased antibody response to vaccination [20]. Temporary discontinuation of MTX for two weeks prior to and two weeks post vaccination can be considered, as this has been shown to significantly improve immunogenicity of influenza vaccination in patients with RA [21].

Traditional immunosuppressive therapies (cyclosporine, mycophenolate mofetil, azathioprine)

Risk of infection

Cyclosporine (CSA), mycophenolate mofetil (MMF), and azathioprine (AZA) all carry the potential for an increased risk of infection based on their suppression of B and/or T cells. The increased risk is best documented in solid organ transplant patients on high-doses and/or multiple immunosuppressive agents [22]. The risk in dermatology patients on monotherapy is less clear. Compared to patients on MTX, adults with AD on CSA demonstrated a decreased 6-month risk of infection (relative risk [RR]:

0.87, 95% CI: 0.59-1.29), [12], whereas adults with psoriasis on CSA had an increased risk of infection (adjusted risk ratio [RR]: 1.58, 95% CI: 1.17-2.15), [23]. Additionally, AD patients on MMF or AZA had triple (relative risk [RR]: 3.31, 95% CI: 1.94-5.64) and double (RR: 1.78, 95% CI: 0.98-3.25) the 6-month infection risk, respectively, compared to those taking MTX [12]. In patients with pemphigus vulgaris (PV), MMF has been associated with an increased risk of infection at doses >2g daily[24] and a possible increased risk of HZ [25].

Vaccine recommendations and safety

Given CSA is often used as a temporary therapy or as a bridge to alternative therapy, it is critical to anticipate and potentially administer required vaccinations for subsequent therapies prior to starting CSA. Administration of the human papillomavirus (HPV) vaccine prior to starting MMF may be beneficial as patients with SLE on MMF had decreased antibody response rates following HPV vaccination [26]. Azathioprine has been associated with a poor response to HBV vaccination in inflammatory bowel disease (IBD) patients, thus HBV vaccination should be considered prior to starting AZA therapy, including in patients with chronic skin diseases [27].

TNF inhibitors and other biologic therapies

Risk of infection

A meta-analysis of patients with plaque psoriasis and psoriatic arthritis concluded that use of anti-tumor necrosis factor (TNF) therapy was associated with a small but significant increased risk of overall infection (odds ratio [OR]: 1.18, 95% CI: 1.05-1.33), [28]. Studies examining data from the BIOBADADERM and PSOLAR registries have similarly observed higher rates of infection in patients on TNF inhibitors (infliximab, adalimumab) versus ustekinumab and non-biologic drugs (methotrexate, systemic retinoids), with the highest risk of infection in infliximab (adjusted risk ratio [RR]: 1.71, 95% CI: 1.1-2.65), [23, 29]. In a meta-analysis of patients on immunosuppressants for RA, psoriasis, psoriatic arthritis, SLE, and IBD, an increased risk of HZ was associated with patients on biologic therapy compared to controls (OR: 1.58, 95% CI: 1.39-1.81), [30]. Etanercept, certolizumab, ustekinumab, secukinumab, ixekizumab, guselkumab, risankizumab, and tildrakizumab all contain a warning on the prescribing insert for an increased risk of upper respiratory infections, whereas adalimumab, certolizumab, etanercept, infliximab, ustekinumab, and risankizumab contain a warning for a possible increased risk of pneumonia. Recent meta-estimates of psoriasis patients observed an elevated risk of respiratory tract infections in interleukin (IL)-17 inhibitors (OR: 1.56, 95% CI: 1.04-2.33), but not in IL23 inhibitors, potentially highlighting the importance of influenza vaccination [31,32]. Rates of upper respiratory infections were similarly increased in psoriasis patients on a TNF inhibitor compared to placebo [33].

Vaccine recommendations and safety

Owing to the increased risk of pneumonia observed in psoriasis patients and decreased antibody response rate to pneumococcal vaccination seen in several meta-analyses [34,35], the NPF and ACR recommend pneumococcal vaccination prior to starting biologic therapy [5-7]. There is some evidence that anti-TNF therapy reduces the response to HBV vaccination through impaired germinal center-dependent B cell maturation [36]. Therefore, anti-TNF therapy should ideally be delayed until four weeks after the first dose of the HBV series in those who need to be vaccinated.

Janus kinase inhibitors

Risk of infection

Janus kinase (JAK) inhibitors are associated with an increased risk of serious infection. In psoriasis patients, tofacitinib monotherapy has been associated with an increased risk of HZ (incidence rate [IR]: 2.55, 95% CI: 2.13-3.03) cases/100 person-years compared to 0 cases/100 person-years in placebo, particularly among patients with older age, prior biologic use, and Asian ethnicity [37]. A retrospective analysis of claims data of RA patients on tofacitinib found rates of HZ to be approximately double those observed in patients on biologics (including abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab) [38].

Vaccine recommendations and safety

Pneumococcal vaccination should be given to all patients on iatrogenic immunosuppression [7].

Vaccination prior to therapy is recommended as patients on tofacitinib have been observed to mount satisfactory immune response to PCV13 but diminished responses to PPSV23, particularly in those taking concomitant MTX [20]. The Shingrix vaccine is especially important in patients 50 years of age and older but should also be considered in those <50 years given the increased risk of HZ reactivation while on a JAK inhibitor [30,37]. In patients with psoriasis treated with tofacitinib, every 10-year increase in age was associated with a 1.3x increased risk of developing HZ (HR: 1.30, 95% CI: 1.10-1.53), [37].

Rituximab

Risk of infection

Normal B cells become profoundly depleted during rituximab therapy and may take up to 12 months after stopping rituximab to recover to pretreatment levels [39]. Patients are therefore considered to be at increased risk of infection for up to 12 months after stopping treatment. The risk of serious infection may further increase with additional cycles of rituximab [40]. Interestingly, in a randomized control trial of pemphigus vulgaris patients taking rituximab and 3-6 month corticosteroid therapy versus 12-18 month corticosteroid monotherapy, similar rates of infection were seen in both groups [41].

Vaccine recommendations and safety

Because response to all vaccinations is significantly impaired while on rituximab and for at least 6 months afterwards, administration of vaccines prior to therapy, ideally four weeks before starting, is important [34,42]. Any additional or follow-up vaccines should be delayed until at least 6 months after rituximab therapy has ended for the best humoral response.

Special situations—travel vaccines

Questions about the safety and efficacy of travel vaccines are typically handled in conjunction with a travel medicine provider. The two most common vaccines recommended for travelers are yellow fever (YF) and hepatitis A virus (HAV) vaccinations, with specific recommendations summarized in **Table 3**.

The live YF vaccine is contraindicated in the setting of immunosuppressive therapies, although observational studies of patients who were inadvertently vaccinated while on MTX, infliximab, and rituximab observed mostly adequate antibody titers and no major adverse events [43]. Although the inactivated HAV vaccine can be safely given during immunomodulatory therapy, administration at least two weeks prior to starting therapy may improve humoral response [44].

Conclusion

As the use of immunosuppressive and immunomodulatory therapies continues to expand in dermatology practice, dermatologists play a critical role in educating patients on the risks of vaccine-preventable illness associated with medications. Beyond providing individualized vaccine counseling, some dermatologists may also be able to improve accessibility of vaccinations through offering vaccines in their offices, partnering with local pharmacies, or providing informational pamphlets detailing where to obtain the vaccine. Although vaccine guidance may not traditionally have fallen to dermatologists, it is an important step we can all take to improve patient care

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Table 1. *Age-appropriate adult vaccine recommendations.*

Vaccine	Tetanus, diphtheria, pertussis	Human papillomavirus	Influenza	Herpes zoster	Pneumococcal	Hepatitis B
Vaccine type	Tdap (tetanus, diphtheria, pertussis): inactivated Td (tetanus, diphtheria): inactivated	9vHPV: 9-valent recombinant	IIV: inactivated RIV: recombinant LAIV: live attenuated	RSV (*preferred*): recombinant ZVL: live	PCV13: 13-valent conjugate PPSV23: 23-valent polysaccharide	HepB: recombinant HepA-HepB: recombinant
High risk populations			Pregnant women, adults >65 years.	Older age, immunosuppression, HIV, leukemia, or lymphoma.	Older age, chronic medical comorbidities, asplenia, immunosuppression.	Chronic liver disease, HIV, those at risk for exposure to blood, incarcerated persons, travel in countries where hepatitis B is common, or pregnancy.
Recommendations	1 dose of Tdap for adults who have never received Tdap, followed by a Tdap or Td booster every 10 years.	A 3-dose series if the first dose is given after age 15. HPV vaccination is recommended through age 26 and in patients aged 27-45 who are at risk for ongoing exposure to HPV.	Persons >6 months should receive the influenza vaccine annually. Adults >65 years should receive the high-dose or adjuvant vaccine.	For adults ≥50 years, a 2-dose series of RSV (Shingrix) is recommended, regardless of previous vaccination with ZVL (Zostavax) and/or history of shingles.	All adults ≥65 years should receive 1 dose PPSV23. Adults 19-64 years under iatrogenic immunosuppression should receive 1 dose PCV13, then 2 doses of PPSV23.	A 2-dose or 3-dose series for previously non-immune, at risk adults

[1]High-dose glucocorticoids: ≥20 mg/day of prednisone for ≥2 weeks. [2]Pneumonia vaccination strategy in patients who are iatrogenically immunosuppressed: PCV13 followed by a dose of PPSV23 at least 8 weeks later.

Table 3. *Travel vaccines.*

Vaccine	Yellow fever	Hepatitis A
Vaccine type	Yellow fever: live	HepA: inactivated HepA-HepB: inactivated-recombinant
At risk individuals	Immunocompetent adults traveling to areas at risk.	Chronic liver disease, HIV, sexual exposure risk, injection or non-injection drug use, homelessness, occupational risk, travelers to endemic areas, or close contact with an international adoptee.
Recommendations	A single dose confers lifelong protection. Vaccination is contraindicated in the setting of immunosuppressive therapies.	A 2-dose series or 3-dose series (HepA-HepB) is recommended.

[1]Recommendations adapted from the CDC guidelines (https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html).