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An evidence-based guide to SARS-CoV-2 vaccination of patients on immunotherapies in dermatology

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Immune-mediated diseases and immunotherapeutics can negatively affect normal immune functioning and, consequently, vaccine safety and response. The COVID-19 pandemic has incited research aimed at developing a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine. As SARS-CoV-2 vaccines are developed and made available, the assessment of anticipated safety and efficacy in patients with immune-mediated dermatologic diseases and requiring immunosuppressive and/or immunomodulatory therapy is particularly important. A review of the literature was conducted by a multidisciplinary committee to provide guidance on the safety and efficacy of SARS-CoV-2 vaccination for dermatologists and other clinicians when prescribing immunotherapeutics. The vaccine platforms being used to develop SARS-CoV-2 vaccines are expected to be safe and potentially effective for dermatology patients on immunotherapeutics. Current guidelines for the vaccination of an immunocompromised host remain appropriate when considering future administration of SARS-CoV-2 vaccines. (J Am Acad Dermatol 2021;84:1652-66.)

Key words: COVID-19; immunomodulatory therapy; immunosuppressive therapy; SARS-CoV-2; vaccine.

Patients with immune-mediated dermatologic diseases can require treatment with short-term and long-term immunosuppressive and/or immunomodulatory therapy. Immune-mediated diseases and immunotherapeutics can negatively affect normal immune functioning, placing these patients at increased risk of infection.[1-3] However, patients on immunotherapies for dermatologic and rheumatologic disease do not appear to be more susceptible to COVID-19.[4]

Vaccines protect against infection by provoking a protective humoral and cellular immune response.[5,6] Assessment of vaccine safety is largely derived from observational studies,[7] whereas the efficacy of vaccination is commonly investigated by using post-immunization antibody titers as correlates of protection.[6,8-10] For patients on immunotherapeutics, clinical decision making regarding vaccination must weigh the anticipated disease protection achieved by immunization against the risk of vaccine-induced adverse events. Meanwhile, the risk of discontinuation or temporary withdrawal of therapy must also be considered because some immunotherapies can carry the risk of increased disease activity, relapse, or loss of response.[3,11]

The COVID-19 pandemic has included a rapid increase in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) research around the globe, particularly research aimed at developing a SARS-CoV-2 vaccine. SARS-CoV-2 vaccination research has resulted in the development of novel vaccine platforms (ie, RNA, DNA, nonreplicating viral vectors, etc).[12,13] Furthermore, SARS-CoV-2 is a novel vaccine target. As SARS-CoV-2 vaccines are developed and made available, the assessment of potential safety and efficacy in this population is particularly important. The launch of SARS-CoV-2 vaccines creates a unique clinical challenge for dermatologists and other clinicians when prescribing immunotherapeutics. We aim to provide guidance on the safety and efficacy of SARS-CoV-2 vaccination for dermatology patients on immunotherapeutics as

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an adjunct to existing guidelines, including the Infectious Diseases Society of America "Clinical Practice Guideline for Vaccination of the Immunocompromised Host."[14] Specifically, this review is intended to serve as a point of reference to assist dermatologists and clinicians when approaching SARS-CoV-2 vaccination and their patients receiving immunotherapeutics through (1) a review of the SARS-CoV-2 vaccines now authorized for distribution (Moderna messenger RNA [mRNA] and Pfizer-BioNTech mRNA) as well as those under development and an outline of the potential risks to patients receiving immunotherapeutics, (2) a summary of current evidence pertaining to the safety and efficacy of nonviral vaccines in patients receiving immunotherapeutics, and (3) an extrapolation of these data to comment on the anticipated safety and efficacy outcomes with the novel SARS-CoV-2 vaccines.

CAPSULE SUMMARY

- The safety and efficacy of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in patients with immune-mediated dermatologic diseases requiring immunotherapeutics is unknown.
- The SARS-CoV-2 vaccines approved and distributed are expected to be safe for patients on immunotherapeutics with some variability in efficacy, depending on the degree of immunosuppression and type of vaccine given.

METHODS

A review of the literature was conducted by a multidisciplinary committee comprising dermatologists (MGK, JD), immunologists (MGK, JD), a rheumatologist (JD), dermatology residents (LMG, BM) and a specialist in virology and vaccination (MS). Studies were identified by performing a search across electronic databases (MEDLINE, Embase, PubMed) and divided into 3 areas of focus based on major search terms in addition to advanced searching within these databases using the following Medical Subject Headings terms: (1) "SARS-CoV-2" or "COVID-19" and "vaccine" or "vaccination"; (2) "vaccine" or "vaccination" and "glucocorticoid" or "prednisone" or "corticosteroid," as well as "vaccine" or "vaccination" and specific systemic immunotherapy ("apremilast," "azathioprine," "cyclosporine," "methotrexate," "mycophenolate mofetil," and "JAK inhibitors"); (3) "vaccine" or "vaccination" and specific biologic agent ("adalimumab," "certolizumab," "etanercept," "infliximab," "ustekinumab," "brodalumab," "ixekizumab," "secukinumab," "guselkumab," "risankizumab," "tildrakizumab," "rituximab," "anakinra," "dupilumab," "omalizumab," and "IVIG"). Additional relevant studies were identified from the reference lists of primary studies and reviews and included based on relevance to these major search terms. Published studies including clinical trials, meta-analyses, systematic reviews, case series, and case reports were reviewed and assessed for content and grading of quality of evidence adapted from Robinson et al[15] to support recommendations. Data were extracted from individual studies and synthesized into tables.

RESULTS AND DISCUSSION

Review of SARS-CoV-2 vaccines under development

To properly assess risks of vaccines against SARS-CoV-2 to patients on immunotherapeutics, it is important to understand the basic mechanisms of the vaccines' platforms. There are more than 90 vaccines against SARS-CoV-2 in development; the wide range of strategies used to stimulate the immune system to develop protective antibodies is summarized in Table I.[5] Live attenuated vaccines are weakened wild-type viruses that have accumulated mutations to diminish their ability to cause disease and therefore pose the highest risk to dermatology patients on immunotherapeutics because of the rare risk of reversion to the original pathogenic infectious agent.[3,16] However, currently, there are no live attenuated SARS-CoV-2 vaccines in phase 2 or phase 3 trials.

Otherwise, there are 3 principal vaccine platforms that have been used to develop already approved vaccines and are considered safe for patients on immunotherapeutics: inactivated vaccines, protein subunit vaccines, and virus-like particle vaccines. These platforms have been used to develop pertussis vaccines, hepatitis B vaccines, and human papilloma virus vaccines. With regard to developmental SARS-CoV-2 vaccines, there is currently 1 protein subunit vaccine in phase 3 trials (NVX-CoV2373, Novavax), which, based on phase 1 and 2 data, appears to be safe, and elicits a strong antibody response.[17] Nonreplicating viral vectors and RNA/DNA vaccines are in phase 3 trials or have completed phase 3 trials and represent novel methods of vaccination.[18-20] Results suggest that these vaccines are safe and have the ability to produce protective antibody responses.[18-24] The data from phase 2 and 3 trials of ChAdOx1/AZD1222 (Oxford-AstraZeneca) (nonreplicating viral vector) and phase 3 trials of mRNA-1273

Abbreviations used:

IL:	interleukin
mRNA:	messenger RNA
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
TNF:	tumor necrosis factor
VAERD:	vaccine-associated enhanced respiratory disease

(Moderna) (mRNA vaccine) and BNT162 (Pfizer-BioNTech) (mRNA vaccine) indicate that these vaccines are safe, with mild to moderate adverse events and the development of antibody responses that are above convalescent serum controls.[18-20] The US Government has prepurchased mRNA-1273 (mRNA vaccine), BNT162 (mRNA vaccine), JNJ-78436735 (Johnson & Johnson) (nonreplicating viral vector), ChAdOx1/AZD1222 (nonreplicating viral vector), NVX-CoV2373 (Novavax) (protein subunit vaccine), and a protein subunit vaccine from Sanofi/GlaxoSmithKline.

Systemic immunotherapies and vaccines

The following dermatology-relevant immune-targeting therapies were reviewed in the setting of studies evaluating the safety and efficacy of nonviral and live vaccines: apremilast, azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, systemic corticosteroids, and JAK inhibitors. No studies evaluated vaccination in patients receiving thalidomide or apremilast; safety has been addressed in the literature on the basis of expert opinion only.[25]

Safety of vaccines in patients receiving nonbiologic systemic immunotherapy. Based on available studies, detailed in Table II,[26-69] the majority of vaccines are safe in patients receiving nonbiologic immunotherapy. There is ultimately good evidence for the safety of nonviral vaccines in patients with dermatologic, autoimmune, or inflammatory disease treated with standard dermatologic doses of immunosuppressive agents, and these are generally well tolerated (Table II). These findings are aligned with current guideline recommendations.[3,70,71]

Efficacy of vaccines in patients receiving systemic immunotherapies. There is a trend toward a decreased immune response and vaccine immunogenicity in patients on systemic immunotherapies, particularly patients receiving azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, or JAK inhibitors (Table II). Studies evaluating vaccine efficacy in patients receiving mycophenolate mofetil and cyclosporine have been primarily conducted in kidney transplant recipients and/or solid organ transplant recipients, in whom the immunosuppressive regimens result in severely disturbed primary and secondary humoral responses and, therefore, an impaired ability to mount a protective immune response.[72] This may not be generalized to patients with dermatology immune disease on dermatologic doses of immunotherapies. The efficacy of inactivated, attenuated, and recombinant vaccines (ie, trivalent [A/H1N1, H3N2, B strain] and pandemic [A/H1N1] influenza vaccine) has been evaluated in patients receiving methotrexate.[73-83] A significant reduction of inactivated and subunit vaccine antibody titers[84] and inadequate sustained response or nonprotective titers on follow-up (at 4 to 12 weeks) has been reported in patients treated with methotrexate.[85] On the other hand, the response appears to improve with second vaccination in studies evaluating influenza[85] and hepatitis A[86] vaccines in patients receiving methotrexate (15-20 mg per week),[85,86] azathioprine, or cyclosporine.[85,87,88] Satisfactory immune responses to influenza vaccine and nonviral vaccine (PPSV23, tetanus toxoid) in JAK inhibitor—treated patients with rheumatoid arthritis[89] and inflammatory bowel disease have been observed when vaccines were administered either before the initiation of therapy[90-93] or after temporary withdrawal of JAK inhibitors 2 to 3 weeks before vaccination,[89,94,95] which is consistent with most consensus guideline recommendations.[3,70,71] Overall, vaccine efficacy may be reduced in patients receiving systemic immune-targeting therapies because of the impaired immune response in these patients; however, temporary withdrawal and/or additional vaccinations may be considered to achieve adequate protection.

Vaccines and biologics

The majority of primary data on the safety and efficacy of vaccines in patients exposed to biologics focuses on tumor necrosis factor (TNF) alpha inhibitors (primarily infliximab and etanercept) and the anti-CD20 monoclonal antibody rituximab.[74,76,77,79,80,83,96-145] Patients with rheumatoid arthritis and inflammatory bowel disease were the most frequently studied populations.[76,77,83,97-101,103,105,108-110,113,114,116,117,120-122,124,126,127,129-131,133-137,139,140,142-146] No studies on the safety or efficacy of vaccination in patients exposed to the following biologics were identified: brodalumab, anakinra, omalizumab, guselkumab, risankizumab, or tildrakizumab (Table III).[147-152]

Vaccination safety in patients on biologics. There have been few serious adverse events reported with vaccination and patients on biologic therapies, and the majority of reported adverse events were unrelated to

Table I. Review of COVID-19 vaccines in development

Type of vaccine (approved examples)	Description	Example companies and phase of development	Anticipated risk to patients on immunotherapeutics
Inactivated virus	SARS-CoV-2 is allowed to replicate in cells and then killed by using chemicals, heat, or radiation	• Sinovac: approved (not in United States) • Sinopharm: approved (not in United States)	None
Live, attenuated virus	SARS-CoV-2 is genetically engineered to limit infection and reproduction	• Serum Institute and Codagenix: phase 1	Low
Protein subunit	SARS-CoV-2 protein is engineered and produced to stimulate antiviral antibodies	• Novavax (NVX-CoV2373): phase 3	None
Virus-like particles	Virus-like structures enter cells like virus to deliver SARS-CoV-2 protein subunit to stimulate immune response	• Medicago/GlaxoSmithKline: phase 3	None
Nonreplicating viral vectors	Nonreplicating engineered viruses, such as adenovirus or vaccinia, that carry genetic code for proteins of the SARS-CoV-2 virus to stimulate an immune response	• University of Oxford/AstraZeneca (ChAdOx1/AZD1222): approved (expected in United States) • Johnson & Johnson (JNJ-78436735): approved in United States	None to minimal
Replicating viral vectors	Weakened versions of carrier viruses, like influenza or measles, that can replicate in the body and carry genetic code for a protein of SARS-CoV-2. Do not usually cause symptoms.	• University of Pittsburgh/Themis Biosciences/Institut Pasteur/Merck: phase 2	Minimal
RNA	RNA is injected into the body that codes for a SARS-CoV-2 protein that is then produced and leads to antibody development.	• Moderna/National Institute of Allergy and Infectious Diseases (mRNA-1273): approved in United States • BioNTech/Fosun Pharma/Pfizer (BNT162): approved in United States	None
DNA	DNA is injected into the body, often in the form of a plasmid, that codes for a SARS-CoV-2 protein that is then produced and leads to antibody development.	• Inovio/International Vaccine Institute: phase 3 • Cadila Healthcare: phase 2 • Osaka University/AnGes/Takara Bio: phase 2	None

SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

vaccination.[96,117,121,153] Aikawa et al[96] reported 1 serious adverse event in a patient on TNF inhibitor therapy who developed invasive pneumococcal disease with bacterial pneumonia 5 months after vaccination, despite seroconverting 6 out of 7 polysaccharide serotypes analyzed. Blauvelt et al[153] reported 1 treatment-related serious event in their dupilumab treatment group: a serum sickness-like reaction that resolved without sequelae.

Vaccine efficacy in patients on biologics. Data pertaining to vaccine efficacy are heterogeneous. Good antibody levels are observed after vaccination for patients on interleukin (IL) 17 (brodalumab, ixekizumab, secukinumab) and IL-4/13 inhibitors (dupilumab). Anti-TNF (adalimumab, certolizumab, etanercept) and anti—IL-12/23 (ustekinumab) biologics have been associated with a significant decrease in antibody levels. Variable data are observed for rituximab. Exposure to TNF inhibitors did not have a significant effect on humoral responses to pneumococcal (PPS23 and PCV13) or influenza vaccination in patients with rheumatoid arthritis.[76,79,83,96,109,115,117,120,121,125,134,137,143,154] Curiously, TNF inhibitor exposure was associated with a reduced humoral response to pneumococcal and influenza vaccination in patients with inflammatory bowel disease.[103,105,110,113,123,124] Belle et al[100] found that treatment with immunomodulators and TNF inhibitors in patients with

Table II. Review of data on systemic immune targeting therapies and vaccines (see Table 2 in van Riel and de Wit[12])

Drug	Type of vaccination	Adverse events	Effects on immunity	Level of evidence
Systemic corticosteroids (prednisone)	Influenza[26-34,73,75,82,113,116,121] PPSV23[35,36,101,117,119,120] Hepatitis B[37] HPV[38] Herpes/varicella zoster (LZV)[39,40,145] Yellow fever[41]	Safe, generally well tolerated. Increased frequency of moderate/severe local reactions compared to healthy control individuals have been observed; as well as a few reports of increased incidence of clinical and/or biochemical parameters of disease flare[30] or increased herpes zoster risk observed in patients on immune-suppressive therapy[39]	Variable effect on immunity: adequate seroprotection and/or no significant suppression of response in several studies and associated with doses up to <10-20 mg/day.[37,38] Reduced seroconversion rates and/or impaired immune response/humoral response noted in a number of studies and, in particular, associated with a high-dose regimen of >20 mg/day.[27,29,35,116] In VZV, long-term seroprotection for VZV at the 2-year follow-up was also observed.[40,145]	A-B
Methotrexate	Influenza: trivalent,[42,43,79,80,146] pandemic (A/H1N1)[44,45,73,76,78,82-84] PPSV23[43,111] PCV7/13[46,120,143] HAV[86,99] HBV[100] Tetanus/diphtheria[102] MMR[1,47-49,74] Herpes/varicella zoster (LZV,[39,50-52,85,93,145] RZV[92]) Yellow fever[53-56,129]	Safe, generally well tolerated with both nonviral and live-attenuated/live vaccines[7,56,57,*,†] Rare risk of systemic rash and fever with live-attenuated/live vaccine (ie, MMR[48,49] and HZV[39,145])	Variable effect on immunity: Most studies involving live-virus vaccines showed no significant effect on children and adult populations and satisfactory vaccine response/adequate seroprotection with a methotrexate dose of 10-25 mg/week. There is some support for improved response with temporary discontinuation and/or second dose. Nonviral vaccine is overall associated with a negative effect on immunogenicity, including reduced humoral response and insufficient protection with a single dose, with the exception of HBV (no significant effect).[86,99,100]	A-B
Azathioprine	Influenza: trivalent,[32,58-60] pandemic (A/H1N1)[61,62,82,84] PPSV23[110,118] PCV13[63,118] HAV[131] HBV[97,100] Tetanus, pertussis[107] Herpes/varicella zoster (LZV)[39,64-66,92] RZV[92] Yellow fever[61]	Safe, consistently well tolerated with nonviral vaccines and live-attenuated/live vaccines	Variable effects on immune response for nonviral and live-attenuated/live vaccines described. Most studies report blunted to impaired immunogenicity for nonviral and live vaccines (eg, reduced humoral response). Comparable response to healthy control individuals also has been observed in pandemic influenza strains[61,82] and HAV[131]	B

Continued

Table II. Cont'd

Drug	Type of vaccination	Adverse events	Effects on immunity	Level of evidence
Cyclosporine	Influenza: trivalent[62] Pandemic (A/H1N1)[44,61,84] Herpes/varicella zoster (LZV)[39,145] Yellow fever[61] PPSV23[72] HAV[67] Tetanus toxoid[72]	Safe, consistently well tolerated with nonviral vaccines and live-attenuated/live vaccines.	Consistent findings describing overall negative effect on immune response with nonviral and live-attenuated/live vaccines (ie, reduced recall humoral response, reduced rates of seroconversion, in vitro cellular immune response).	A-B
Mycophenolate mofetil	Influenza: trivalent,[59,87] pandemic (A/H1N1)[68,84,88] PPSV23[72] Tetanus toxoid[72] Yellow fever[61]	Safe, generally well tolerated (few reports of mild adverse effects)	Variable effects on immune response described in the literature. Most studies describe reduced immunogenicity/reduced humoral response with nonviral vaccines and worse with doses >2 g/day. Some support for antibody response comparable to healthy control individuals or nonsignificantly reduced/improved response with second dose. No studies evaluating immunogenicity in live-attenuated or live vaccines.	A-B
JAK inhibitors	Influenza (trivalent)[95] PPSV23[89,94,95] Tetanus toxoid[89,95] Herpes/varicella zoster[69,91,92]	No reports of clinically significant adverse effects	Evidence is limited. Overall consistently preserved immunogenicity with nonviral and live-attenuated/live vaccine (ie, LZV[†]); sustained/long-term seroprotection may be inadequate.[‡]	B

HAV, Hepatitis A vaccine; *LZV*, live zoster vaccine; *MMR*, measles, mumps, rubella; *PPSV*, pneumococcal polysaccharide vaccine; *RZV*, recombinant zoster vaccine; *VZV*, Varicella zoster virus.

*No significant adverse effects and no reports of increased clinical or laboratory index of disease activity. No exacerbation of disease activity in a number for autoimmune/inflammatory diseases. No adverse effects in function or graft failure in solid organ transplant recipients. One case report of fatal vaccine-associated viscerotropic disease.[74,83]

[†]In a cohort of patients vaccinated 2 to 3 weeks before starting tofacitinib treatment.

[‡]Diminished humoral response to tetanus toxoid vaccine at week 12 and only 60% mounting 4-fold response to tetanus toxoid vaccine in patients with psoriasis on JAK inhibitors.

inflammatory bowel disease did not influence humoral response to hepatitis B vaccination compared to healthy control individuals.[100] Patients with moderate to severe psoriasis treated with ustekinumab did not experience a change in humoral response to PPSV23 and tetanus toxoid vaccination.[155] This is further supported by a recent study showing decreased efficacy of influenza vaccination in patients treated with adalimumab but not ustekinumab.[156] In patients exposed to rituximab, most studies found a reduced humoral response to pneumococcal,[101,112,115,126-128,135,157] hepatitis B,[136] and influenza vaccination.[73,108,111,116,122,130,142,144] Rituximab exposure did not significantly affect humoral response to seasonal influenza vaccination in patients with autoimmune blistering disease.[104] Blauvelt et al[153] found that patients with moderate to severe atopic dermatitis treated with dupilumab did not have a decreased humoral response to meningococcal and tetanus/diphtheria/pertussis vaccination.

Table III. Review of data on vaccines and biologics*,†

Drug	Type of vaccination	Adverse events	Effects on immunity	Level of evidence
Adalimumab (TNF inhibitor)	PPSV23[117] Influenza[117,156] HBV[114,133]	Safe, generally well tolerated	Variable; some studies show no significant effect on humoral response,[117,133] while others show reduced humoral response.[114,117,156]	A-B
Certolizumab (TNF inhibitor)[121]	Influenza PPSV23	Safe, generally well tolerated	No significant effect on humoral response	A
Etanercept (TNF inhibitor)	MMR[74] PPSV23[96,125] PCV13[134] Influenza[106] HBV[114,136]	Safe, generally well tolerated No increase in disease activity	Variable; most studies showed no significant effect on humoral response,[96,125,134] while some showed reduced humoral response.[73,106,114]	A-B
Infliximab (TNF inhibitor)	Influenza[76,105,109,113,124] HBV[97,114,133,136] Yellow fever[129,139] PPSV23[110,143]	Safe, generally well tolerated No increase in disease activity	Variable efficacy for trivalent influenza and PPSV23 vaccination. Some studies show no significant effect on humoral response,[76,109,124] while others show reduced humoral response.[105,110,113,124] Most studies showed reduced humoral response to HBV vaccination.[97,114,133] Adequate humoral response to yellow fever vaccination.	A-B C*
TNF inhibitors grouped	HBV[100,133,138] HAV[99,103,131] HZ[145] PPSV23[103,120,123,138] PCV13[115,118,126,128,147] Tdap[102,107] Influenza[79,80,115,116,122,137,140,154] Pandemic (A/H1N1)[77,83,103]	Safe, well tolerated No increase in disease activity	Variable; some studies show no significant effect on humoral response, while others show reduced humoral response. Vaccine possibly associated with lower HZ incidence 2 years after vaccination.[145] No significant difference in humoral response to PPSV23 vaccine between infliximab or etanercept treated patients.[138]	A-B
Ustekinumab (IL-12/23 inhibitor)	Influenza[156] PPSV23[155] Tetanus toxoid[155] HBV[114]	N/A	Nonimpaired immune response and efficacy of inactivated influenza vaccine. No significant effect on humoral response to PPSV23 and tetanus vaccination. Possible reduced humoral response to HBV vaccination	A-B
Ixekizumab (IL-17 inhibitor)	PPSV23[148] Tetanus toxoid[148]	Well tolerated	No significant effect to humoral response	A
Secukinumab (IL-17 inhibitor)	Meningococcal C Conjugate[149] Trivalent influenza[136,149,150]	Well tolerated No increase in disease activity	No significant effect to humoral response	A-B
Rituximab (anti—CD-20)	Influenza[98,104,108,111,115,116,122,130,135,142,144] PPSV23[101,115,135] PCV13[112,126-128] PCV7[157] TdaP[102] Yellow fever[129] HBV[136] HZ[145]	Well tolerated No increase in disease activity	The majority of studies found a reduced humoral response to influenza, pneumococcal, HBV, and TdaP vaccine. Vaccination possibly associated with significantly lower HZ incidence 2 years after vaccination.[145] No significant effect on humoral response to yellow fever vaccination.	A-B C*

Dupilumab (IL-4/13 inhibitor)	TdaP	Safe, well tolerated	No significant effect on humoral response	A
	MPSV4[153]			
IVIG	MMR[151]	N/A	No significant effect on humoral response when vaccination occurs before IVIG administration. Decreased humoral response when vaccination occurs after IVIG administration.	B
	Influenza[152]			

HAV, Hepatitis A vaccine; *HBV*, hepatitis B virus; *HZ*, herpes zoster; *IL*, interleukin; *IVIG*, intravenous immunoglobulin; *MMR*, measles, mumps, rubella; *MPSV*, meningococcal polysaccharide vaccine; *N/A*, not applicable; *PCV*, pneumococcal conjugate vaccine; *PPSV*, pneumococcal polysaccharide vaccine; *TdaP*, tetanus/diphtheria/pertussis; *TNF*, tumor necrosis factor.
*The only study with level of evidence C is Oliveira et al.[129]
†There were no studies identified evaluating vaccine safety and/or efficacy with following biologics: brodalumab (IL-17 inhibitor), guselkumab (IL-23 inhibitor), risankizumab (IL-23 inhibitor), tildrakizumab (IL-23 inhibitor), anakinra (IL-1 inhibitor), omalizumab.

SARS-CoV-2 candidate vaccines and immunotherapeutics: estimating risk and response

It is not possible to determine the true risk associated with any potential SARS-CoV-2 vaccine until it has gone through all phases of clinical trials and real-world evidence has been gathered from a widely distributed and adopted vaccination program. Nonetheless, we are able to estimate risk from the limited trial data for the SARS-CoV-2 vaccines and from a review of the literature for patients on immunotherapeutics and established vaccines (Fig 1). Considering the immunologic basis of the SARS-CoV-2 vaccine platforms in late-stage development, the estimated risk to patients on immunotherapies is low. From the review of the literature, patients on biologics have no abnormal immune responses leading to detrimental outcomes (Table III). The safety of a potential SARS-CoV-2 vaccine can be estimated based on the mechanism of action of the biologic or on inferences from the limited data on other biologics. For instance, there are no safety or efficacy data for vaccination of patients on anti—IL-23 biologics, but we can infer the safety profile from vaccination of patients on anti—IL-17 biologics and anti—IL-12/23 biologics. Omalizumab, which blocks immunoglobulin E, is also regarded as safe based on the mechanism of action. For the systemic immunotherapeutics, systemic corticosteroids, methotrexate, and JAK inhibitors appear to have the highest risk of reduced antibody production. However, it should be noted that in previous reviews, methotrexate and JAK inhibitors were considered safe therapies during the COVID-19 pandemic and, in fact, are being studied as potential treatments for COVID-19.[158,159]

With regard to vaccine-generated antibody response, data generally support a possible decrease in antibody titers with the TNF-αbiologics, rituximab, ustekinumab, and many of the oral immunotherapies.[3] Given the possibility of decreased antibody titers to vaccination with some of these treatments, there have been suggestions for withholding immunotherapeutics at the time of vaccination to promote a better vaccine response.[157] For instance, a 2-week temporary withdrawal of methotrexate after vaccination for influenza has been shown to result in higher antibody titers in patients with rheumatoid arthritis.[160] It would thus be prudent to check the titers after vaccination for any patients on a immunotherapeutic because they might require a booster to establish or maintain protective antibody titers. If protective antibody titers are inadequate and skewed to a T helper type 2 phenotype, vaccine-associated enhanced

	Inactivated virus	Live, attenuated virus	Protein subunit	Virus-like particles	Nonreplicating viral vectors	Replicating viral vectors	RNA	DNA
Apremilast*	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++
Azathioprine	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Cyclosporine	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Methotrexate	+/-	+	+/-	+/-	+/-	+/-	+/-	+/-
Mycophenolate mofetil	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Thalidomide*	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++
JAK inhibitors	+	+	+	+	+	+	+	+
Systemic corticosteroids	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Anti-TNF (adalimumab, certolizumab, etanercept)	+	+	+	+	+	+	+	+
Anti–IL-17 (brodalumab, ixekizumab, secukinumab)	++	++	++	++	++	++	++	++
Anti–IL-12/23 (ustekinumab)	+	+	+	+	+	+	+	+
Anti–IL-23* (guselkumab, risankizumab, tildrakizumab)	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++
Rituximab (anti-CD20)	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Anakinra* (IL-1 inhibitor)	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++
Dupilumab (IL-4/13 inhibitor)	++	++	++	++	++	++	++	++
Omalizumab	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++
IVIG	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++	Likely ++

IL, Interleukin; *IVIG,* intravenous immunoglobulin; *TNF,* tumor necrosis factor.

Legend: ++, good antibody levels; +, fair antibody levels with some reports of decreased antibody levels; +/-, variable antibody levels

No to minimal risk	
Minimal risk	
Low risk	
High risk	

Fig 1. Summary of the safety and efficacy for potential SARS-CoV-2 vaccines for patients on immunotherapeutics. *Insufficient data. There were no studies evaluating the safety and/or efficacy of vaccination in patients receiving thalidomide, apremilast, IVIg, or the following biologics: brodalumab, anakinra, omalizumab, guselkumab, risankizumab, or tildrakizumab. Data on apremilast has been addressed in the literature on the basis of expert opinion only.

Box 1. Summary of the recommendations for vaccination as applied to a potential SARS-CoV-2 vaccine

1. Nonviral or inactivated SARS-CoV-2 vaccine subtypes may be considered before, during, or after immunosuppressive therapy in patients receiving systemic immunosuppressant or immune-targeting therapy without significant modification of ongoing treatments.
   1.1. Safety: minimal to no risk of adverse events
   1.2. Efficacy: variable antibody levels expected depending on vaccine and immunotherapy
2. Nonviral SARS-CoV-2 vaccine subtypes may be considered in patients receiving biologic therapy without significant modification of ongoing immune therapy.
   2.1. Safety: minimal to no risk of adverse events
   2.2. Efficacy: at least fair to good antibody response for most biologics
3. The risk-to-benefit ratio may favor immunization if immunosuppression is low and there is significant risk of disease development.
4. Consider checking antibody titers after vaccination and using additional vaccinations, if needed, to boost the level of protective antibodies.

SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

respiratory disease (VAERD) can develop.[161] VAERD is a condition in which vaccination makes subsequent infections with the same virus worse. VAERD has been noted with vaccines to respiratory syncytial virus[162] and measles,[163] as well as vaccination in animal models of Middle East respiratory syndrome coronavirus (MERS-CoV).[164] Based on the data from the current SARS-CoV-2 vaccines, the risk of VAERD appears to be low in the absence of immune modulatory therapy,[22-24,165] but the possibility of T helper type 2 deviation may need to be considered. Otherwise, general considerations of vaccine safety need to be considered, such as allergic or anaphylactic reactions and exuberant inflammatory responses with fever and systemic symptoms. The benefit-to-risk ratio for vaccinating patients for SARS-CoV-2 is ultimately a discussion that needs to involve informed clinicians and patients.

Study limitations

This article provides an overview of current evidence on the administration of existing approved vaccines in patients receiving immunotherapy. Consequently, information is subject to process bias secondary to the methodology of the review. Existing evidence is frequently of low/limited quality with a lack of control groups, insufficient sample size and therefore limited power, and/or inconsistent findings. There is a paucity of data pertaining to vaccination in patient populations on immunosuppressive and immunomodulatory therapies, especially patients with dermatologic disease. Moreover, there is variability of underlying disease or treatment in study populations, which reflects the current diversity of immunosuppressive and immunomodulatory medications and the range of combinations in treatment regimens.

RECOMMENDATIONS AND CONCLUSIONS

The data reviewed in this article support the safety and potential efficacy of SARS-CoV-2 vaccines for our dermatology patients on immunotherapies (Box 1). The SARS-CoV-2 vaccines currently approved (Moderna/NIAID mRNA-1273, Pfizer/BioNTech/Fosun Pharma BNT162) and most likely to be approved (Astra-Zeneca/University of Oxford ChAdOx1/AZD1222, Johnson & Johnson JNJ-78436735, Novavax NVX-CoV2373) in North America are vaccine platforms (ie, RNA, protein subunit, and nonreplicating viral vectors) that are expected to be safe for patients on immunotherapeutics. The anticipated efficacy is variable in the setting of systemic immunotherapies. Although most biologics are associated with good (anti-IL-17, anti-IL-4/13) to fair (anti-TNF, anti-IL-12/23) antibody response to all vaccine subtypes, there is paucity in data for a number of agents. The current Infectious Diseases Society of America "Clinical Practice Guideline for Vaccination of the Immunocompromised Host" remains appropriate when considering future administration of a SARS-CoV-2 vaccine,[14] although additional vaccinations and monitoring antibody titers can be considered.

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Conflicts of interest

None disclosed.

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