REVIEW ARTICLE

SARS-CoV-2 (COVID-19) vaccination in dermatology patients on immunomodulatory and biologic agents: Recommendations from the Australasian Medical Dermatology Group

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ABSTRACT

As the phase III COVID-19 vaccine trials excluded patients on immunosuppressive treatments, or patients with significant autoimmunity, the Australasian Medical Dermatology Group make the following preliminary recommendations around COVID-19 vaccination in dermatology patients on immunomodulatory and/or biologic agents.

- Vaccination against COVID-19 is strongly encouraged for all patients on immunomodulatory drugs and/or biologic agents.
- There are currently insufficient data to recommend one COVID-19 vaccine or vaccine type (mRNA, recombinant, inactivated virus) over another.
- No specific additional risk in patients on immunomodulatory or biologic therapies has so far been identified.
- Data on vaccine efficacy in patients on immunomodulatory or biologic therapies are missing, so standard vaccination protocols are recommended until otherwise advised.

Key words: biologic therapies, COVID-19, dermatology, immunomodulatory therapies, immunosuppressive therapies, SARS-CoV-2, vaccine.

INTRODUCTION

The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has accelerated vaccine development, with several vaccine candidates already attaining emergency or formal regulatory approval. Although COVID-19 vaccines such as BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna) and AZD1222 (Oxford/Astra Zeneca) have demonstrated high vaccine efficacy and a safety profile comparable to other vaccines, pivotal trials have excluded the immunocompromised or those on immunomodulatory treatments.[1,2,3] As countries roll out mass vaccination programmes for the general population, guidance is needed for dermatology patients on immunomodulatory and/or biologic agents.

We formulated these recommendations based on expert opinion,[4] clinical experience and review of clinical data from key phase III COVID-19 vaccination trials.

SUMMARY OF APPROVED COVID-19 VACCINATIONS

The Australian and New Zealand governments have entered into various supply agreements for BNT162b2, AZD1222, NVX-CoV2373 (Novavax) and, additionally in New Zealand, D26.COV2.S (Janssen Pharmaceutica) vaccines. There is currently no agreement for mRNA-1273; however, it may be purchased as part of the agreement

with COVAX facility (https://www.who.int/initiatives/act-accelerator/covax).

In phase III trials, mRNA vaccines (BNT162b2 and mRNA-1273) have demonstrated high efficacy in preventing new, symptomatic COVID-19 infection (up to 95%) and may also impart protection against severe COVID disease.[1,2] Although results are promising, there are logistical challenges for mass vaccination with mRNA vaccines, including a higher manufacture cost and the need for ultra-low temperature cold chain. Furthermore, it is unclear whether these regulatory approved vaccines will be as efficacious against newer strains of SARS-CoV-2 (e.g. B.1.1.7, B.1.351 and P.1 variants). There are also insufficient data to determine whether asymptomatic transmission of SARS-CoV-2 can still occur in immunised individuals.

Phase III results for the adenovirus vector vaccine AZD1222 showed an overall vaccine efficacy of 70%; however, trial limitations included variable timing of booster dosing and a low proportion of elderly subjects.[5] Preliminary results for the recombinant protein subunit vaccine, NVX-CoV2373, from its phase III trial are favourable with vaccine efficacy of nearly 90%; however, trial results are not yet published.

Notably, all aforementioned phase III vaccine trials had limited numbers of patients on immunomodulatory treatments or patients with significant immunosuppression or autoimmunity. Currently, the vaccines in late-phase trials are non-live or utilise a replication-deficient viral vector, and would be compatible for use in patients on immunomodulatory treatments or biologic agents, but it is possible that live-vaccine candidates will progress to clinical trials. The efficacy and safety of vaccines in completed phase III trials are summarised in Table 1, and other vaccines in phase III trials are listed in Table 2.

The most frequent adverse reactions in the COVID-19 vaccine trials were pain at the injection site, fatigue, headache, myalgia, chills, arthralgia and fever; these were each reported in more than 1 in 10 people, which is higher than usual for vaccines.[1,2] Within 24 h of the commencement of the UK mass vaccination programme, two reports of anaphylactoid reactions to BNT162b2 were reported in patients with significant history of anaphylaxis.[5] Widespread use of the vaccine so far suggests that severe allergic reactions are very rare, with initial reported rates of around 1–2 in 100 000 doses.[6] It remains unknown whether atopy or autoimmunity increases this risk.

Cutaneous reactions to COVID-19 vaccines are common, particularly injection site erythema and swelling, occurring in around 5–10% from the mRNA vaccine trials.[1,2] These have largely been mild and self-limiting, with no reported grade 4 local reactions in trials. Other cutaneous reactions have been rare in phase III trials and not significantly more frequent than in the control groups.[2] Table 3 summarises commonly reported cutaneous reactions from the UK Yellow Card vaccine-monitoring programme.[6] Notably, there are several reports of urticaria, and rare cases of erythema multiforme/Steven–Johnson syndrome/toxic epidermal necrolysis reported in the BNT162b2 vaccination programme;

however, causality for any of the reported reactions has not been established.

PRELIMINARY RECOMMENDATIONS

Despite the limited clinical trial data, we make the following preliminary recommendations based on many years of safety data for other vaccines including seasonal influenza, human papillomavirus and the recombinant herpes zoster vaccines, in these patient groups.

Indications and contraindications for COVID-19 vaccination

- We consider all dermatology patients on immunomodulatory or biologic therapies as vulnerable, and vaccination should strongly be encouraged.

  a Reports from the beginning of the pandemic suggested that the severity of COVID-19 illness was not significantly worse in patients on immune-mediated therapies.[7,8] Subsequent analysis of data from psoriasis registries such as Biobadaderm reported a slightly higher rate of COVID-19, hospitalisation, ICU admission and death in patients with psoriasis on systemic therapy compared to the general population, although this was not statistically significant.[9]
  b Nevertheless, many dermatology patients will be at higher risk of severe COVID-19 illness, such as those being treated for atopic dermatitis, immunobullous disorders, vasculitis and cutaneous drug eruptions.

- Non-live COVID-19 vaccines should strongly be recommended for most patients on immunomodulatory or biologic agents, unless there are contraindications, such as:

  a History of anaphylaxis or severe allergic reactions to vaccines or excipients such as polyethylene glycol (most recent estimated rate of anaphylaxis being 2.5–5.0 cases per million).

- There are limited data on the safety/efficacy for any of the COVID-19 vaccines during pregnancy, although no red flags have been raised in >10 000 pregnant women who have been vaccinated to date.
- Patients should be counselled to the limited safety and efficacy profile of COVID-19 vaccines in immunocompromised patients, including those suffering from autoimmune disorders, although immunosuppression and autoimmunity are not a safety contraindication at this stage.

Vaccine efficacy in the immunocompromised

- Although there are no direct supporting data, based on studies with other vaccines, there is a concern that some immunomodulators, particularly if more than one is being used, may diminish COVID-19 vaccine efficacy.

  a Anti-TNF agents have been associated with impaired vaccine efficacy for hepatitis B, hepatitis A,

Table 1 Phase III data for COVID-19 vaccines under regulatory approval or consideration in Australia/New Zealand

Vaccine	Dosing	Vaccine platform	Pivotal trial data	Efficacy data	Reactogenicity data	Other safety data
BNT162b2 (Pfizer)	2 doses, 21 days apart	Nucleoside-modified mRNA encoding SARS-CoV-2 prefusion stabilised spike protein	Polack et al. 2020 Multinational, phase II/III, observe blind, placebo controlled N = 43 448 (21 720 received BNT162b2) 2 months of follow-up	94.6% vaccine efficacy Severe COVID •10 (placebo) vs. 1 case (vaccine)	Injection site reactions •80% in 16- to 55-year-old group for each dose •70% in > 55-year-old group for each dose •No grade 4 injection site reactionsSystemic reactions •Occurred more frequently after second dose and in the 16- to 55-year-old group •Fatigue 50-60% after second dose •Headache 40-50% after second dose •Fever 16% in (16- to 55-year-old group), 11% (>55-year-old group)	Overall adverse event rate •27% (vaccine) vs. 12% (placebo)Serious adverse event rate •0.6% (vaccine) vs. 0.5% (placebo)No vaccine-related deaths
mRNA-1273 (Moderna)	2 doses, 28 days apart	mRNA encoding prefusion stabilised spike protein	US-based, phase II/III, observer blind, placebo controlled N = 30 420 (15 210 received mRNA-1273) Median follow-up 63 days	94.1% vaccine efficacy Severe COVID •30 cases (placebo) vs. 0 (vaccine)	Injection site reactions •85% for both dosesSystemic reaction (myalgia, headache, fatigue) •Occurred more frequently after second dose, in around 80%, •Headache, myalgia and fatigue most commonly reported •Lasted median duration of 3 daysBoth injection site and systemic reactions were more common in younger participants	Serious adverse event rate •1.5% (vaccine) vs. 1.3% (placebo) Hypersensitivity reaction •1.5% (vaccine) vs. 1.1% (placebo)3 cases of Bell's palsy in vaccine group No vaccine-related deaths
AZD1222 (Oxford-Astra Zeneca)	2 doses, 28 days apart	Replication-deficient chimpanzee adenoviral vector containing SARS-CoV-2 spike protein	Pooled data from 2 phase III trials (COV002 and COV003) n = 11 636 for primary efficacy end point analysis Median follow-up 3.4 months	70.4% vaccine efficacy (up to 90% in half-dose/standard dose subgroup) Severe COVID •2 cases (control) vs. 0 (vaccine) Hospitalised COVID •10 cases (control) vs. 0 (vaccine)	Not reported in pooled analysis	Serious adverse event rate •0.8% (vaccine) vs. 0.7% (control)2 cases of transverse myelitis in vaccine group deemed unrelated No vaccine-related deaths

pneumococcal and influenza in inflammatory bowel disease,[10,11] although vaccination responses are relatively preserved when anti-TNF agents are used in rheumatoid arthritis.[12,13]

b There is a consistent body of evidence that methotrexate impairs humoral response when used as monotherapy or in combination with a biologic.[12]

c An early case–control study indicated that ciclosporin impairs response to influenza vaccination in renal transplant recipients.[14]

d Prednisolone at 10 mg/day or more was found to diminish humoral responses to influenza vaccines in patients with systemic lupus erythematosus.[15]

e Patients starting tofacitinib had diminished responsiveness to pneumococcal polysaccharide vaccine

Table 2 Vaccine candidate in phase III trials

Vaccine	Vaccine platform	Manufacturer
NVX-CoV2373	Protein subunit (recombinant)	Novavax
Ad5-nCOV	Non-replicating viral vector	CanSino
Ad26.COV2.S	Non-replicating viral vector	Johnson and Johnson (Janssen Pharmaceutica)
INO-4800	DNA plasmid vaccine	Inovio Pharmaceuticals
CoronaVac	Inactivated virus	Sinovac
Gam-COVID-Vac/Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Russia)
BBV152/ Covaxin	Inactivated virus	Bharat Biotech International Limited)
BBIBP-CorV	Inactivated virus	Chinese Ministry of Science and Technology
ZF2001	Protein subunit	Anhui Zhifei Longcom Biologic Pharmacy
EpiVacCorona	Peptide Vaccine	Vektor State Research Centre of Virology and Biotechnology
ZyCOV-D	Plasmid DNA Vaccine	Zydus Cadila

Table 3 Dermatology adverse effects of COVID-19 vaccines from the UK Yellow Card Programme[6] (causality has not been established yet)

BNT162b2	AZD1222
Commonly reported (>100 reports): Rash Pruritus Erythema Hyperhidrosis Urticaria Cold sweat Night sweatsSerious cutaneous reactions: 1 case of toxic epidermal necrolysis with fatality 3 cases of erythema multiforme 1 case of Stevens–Johnson syndrome	Commonly reported (>100 reports): Hyperhidrosis Rash PruritusSerious cutaneous reactions: 1 case of allergic dermatitis with fatality

(PPSV-23), but not influenza vaccine, particularly in those taking concomitant methotrexate.[16]

f Rituximab severely impairs vaccine responses for at least 6 months due to its B-cell depleting effects.[17]

g Several patients with COVID-19, treated with hydroxychloroquine/chloroquine, had lower IgG antibody responses than expected on recovery.[18]

h Satisfactory humoral response to PCV13 at 4 weeks occurred in ~two-thirds of patients with rheumatoid arthritis receiving long-term treatment with upadacitinib and background methotrexate, which was similar to placebo.[19]

• Limited studies on newer generation biologic agents used in chronic plaque psoriasis and atopic dermatitis suggest little to no interference to seasonal influenza, pneumococcal or tetanus vaccine.

   a Ustekinumab was associated with preserved immune responses to pneumococcal and tetanus vaccines based on antibody levels in the PHOENIX 2 long-term extension trial.[20]

   b In two small studies on secukinumab in psoriasis and psoriatic arthritis, secukinumab did not interfere with influenza or meningococcal vaccination efficacy in terms of antibody titre increase.[21,22]

   c In a phase I trial, antibody responses to tetanus vaccine in patients initiated on ixekizumab were similar between ixekizumab and control groups.[23]

   d No data are available for IL-23 inhibitors on the response to non-live vaccines.

   e Dupilumab did not affect responses to tetanus and meningococcal vaccines, IgE seroconversion to tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccination.[24]

• Due to a lack of data in the immunocompromised, no particular COVID-19 vaccine or vaccine type (mRNA, recombinant, inactivated virus) is considered superior or preferred at this stage.

• Current effective immunomodulatory therapy should not be stopped prior to vaccination, as uncontrolled disease activity may lead to disease-related complications and there is currently no evidence to suggest that short-term washout would enhance COVID-19 vaccine immune response.

• Currently, there is no known role for additional vaccine dosing or neutralising antibody titre testing for vaccine efficacy in patients on immunomodulatory treatments.

• Social distancing and personal hygiene measures to reduce transmission risk should be reinforced in light of a possibly reduced vaccine response in patients on immunomodulatory treatments.

• There is a theoretical risk that asymptomatic transmission of SARS-CoV-2 may be greater in patients on immunomodulatory drugs, even when successfully immunised.

• Vaccination of the patient's direct contacts should be strongly encouraged to maximise local herd immunity.

Timing of COVID-19 vaccination

• If initiation of an immunomodulator or biologic is foreseeable or planned, COVID-19 vaccination, as well as other standard vaccinations (e.g. influenza, pneumococcal, herpes zoster, hepatitis B), should be expedited and given prior to initiation in order to maximise vaccine response.

• In patients who are on a biologic or immunomodulatory agent and have not been vaccinated, it is suggested that, for the currently regulatory approved COVID-19 vaccines, vaccination should be administered at least 7 days either side of biologic/immunomodulator dosing and at a

different anatomical location due to the high frequency of local and systemic reactions.

- At this stage, there are no data on the timing of co-administration of other vaccines (e.g. seasonal influenza, herpes zoster vaccines) with COVID-19 vaccines. The current empiric advice is to administer other vaccines either at least 7 days before COVID-19 vaccination or at least 7 days after the completion of the two-dose COVID-19 vaccine regimen.

OTHER FACTORS TO CONSIDER

With limited supply of vaccines, it will be necessary to prioritise some patients over others. This should be based on clinical risk (i.e. those at increased risk of acquiring disease or increased risk of developing more severe disease) and will need to take into account socioeconomic factors, age, ethnicity, co-morbidities, etc.

We strongly encourage all dermatologists and their staff be vaccinated against SARS-CoV-2 to minimise risk to their patients. However, it remains essential to continue good clinical practice, mask wearing and adherence to local alert levels COVID-19 guidance, as transmission of SARS-CoV-2 can still occur despite immunisation.

There are considerable gaps in the data to make evidence-based decision; it is doubtful that this will become available through randomised clinical trials, so there is a crucial role for disease and therapy registries, both national and multi-national, to track outcome and performance in these patient groups. Given the common use of immunomodulatory and biologic agents across specialities, sharing of opinion and experience with COVID-19 vaccine regimens is important. Combined experience increases understanding of safe and appropriate use of vaccines and may identify specific vaccine and/or disease efficacy issues or reactions.

There are no data on whether the COVID-19 vaccines will influence COVID-19-associated multisystem inflammatory disorder in children or young adults; none of the approved COVID-19 vaccines are currently licensed for use in children under 17 years of age.

Data on vaccine-associated enhanced disease (VAED), particularly if vaccine supply issues result in patients receiving two different COVID-19 vaccines (as opposed to two doses of the same vaccine), are also missing: vaccine-associated enhanced diseases are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen.

CONCLUSION

Large data gaps remain around all the COVID-19 vaccines. Due to the limited number of patients on immunomodulatory treatments in COVID-19 vaccine trials, recommendations can only be made based on empirical evidence. Therefore, anticipate the likelihood that vaccine advice will change as data become available. Currently, COVID-19 vaccination should be strongly recommended to patients on immunomodulatory and/or biologic therapies (and their direct contacts), as no specific contraindication or identifiable safety issues have been identified in this patient group to date. Nevertheless, discussion outlining the limited efficacy and safety profile prior to vaccination is essential for all patients. Adherence to social distancing and hygiene measures remains imperative, as patients should not solely rely on vaccine-mediated protection given the theoretical possibility of a diminished vaccine response, particularly in patients taking conventional immunomodulators including systemic corticosteroids.

REFERENCES

1. Polack F, Thomas S, Kitchin N *et al*. Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. *N. Engl. J. Med.* 2020; **383**: 2603–15.
2. Baden L, Sahly H, Essink B *et al*. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N. Engl. J. Med.* 2021; **384**: 403–16.
3. Voysey M, Clemens S, Madhi S *et al*. Safety and efficacy of the ChAdOx1 nCOV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2020; **397**: 99–111.
4. Wang C, Rademaker M, Baker C *et al*. COVID-19 and the use of immunomodulatory and biologic agents for severe cutaneous disease: an Australian/New Zealand consensus statement. *Australas J. Dermatol.* 2020; **61**: 210–6.
5. Castellis M, Phillips E. Maintaining safety with SARS-CoV-2 vaccines. *N. Engl. J. Med.* 2021; **384**: 643–9. https://doi.org/10.1056/NEJMra2035343
6. Medicine and Healthcare products Regulatory agency. Coronavirus vaccine – Summary of Yellow Card Reporting. UK Government 2021 [updated 2021 Feb 5; cited 2021 Feb 7]. Available from URL: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting
7. Haberman R, Chen A, Castillo R *et al*. COVID-19 in immune-mediated inflammatory diseases – case series from New York. *N. Engl. J. Med.* 2020; **383**: 85–8.
8. Gisondi P, Zaza G, Giglio M *et al*. Risk of hospitalization and death from COVID-19 infection in patients with chronic plaques psoriasis receiving a biologic treatment and renal transplant recipients in maintenance immunosuppressive treatment. *J. Am. Acad. Dermatol.* 2020; **83**: 285–7.
9. Baniandres-Rodriquez O, Vilar-Alejo J, Rivera R *et al*. Incidence of severe COVID-19 outcomes in psoriatic patients treated with systemic therapies during the pandemic: a Biobadaderm cohort analysis. *J. Am. Acad. Dermatol.* 2021; **84**: 513–7.
10. Alexander J, Moran G, Gaya D *et al*. SARS-CoV-2 vaccination for patients with inflammatory bowel disease: a British Society

of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement. *Lancet Gastroenterol. Hepatol.* 2021; **6**: P218–24. https://doi.org/10.1016/S2468-1253(21)00024-8

11. Carrera E, Manzano R, Garrido E. Efficacy of the vaccination in inflammatory bowel disease. *World J. Gastroenterol.* 2013; **19**: 1349–53.

12. Chiricozzi A, Gisondi P, Bellinato F *et al.* Immune response to vaccination in patients with psoriasis treated with systemic therapies. *Vaccines (Basel)* 2020. https://doi.org/10.3390/vaccines8040769.

13. Kapetanovic M, Saxne T, Sjoeholm A *et al.* Influence of methotrexate, TNF blockers and prednisolone on antibody response to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology* 2006; **45**: 106–11.

14. Versluis D, Beyer W, Masurel N *et al.* Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation* 1986; **42**: 376–9.

15. Papp K, Boulos H, Kumar D *et al.* Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. *J. Cutan. Med. Surg.* 2018; **23**: 50–74.

16. Winthrop KL, Silverfield J, Racewicz A *et al.* The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann. Rheum. Dis.* 2016; **75**: 687–95.

17. Nazi I, Kelton J, Larche M *et al.* The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. *Blood* 2013; **122**: 1946–53.

18. de Miranda Santos IKF, Costa CHN. Impact of hydroxychloroquine on antibody responses to the SARS-CoV-2 coronavirus. *Front. Immunol.* 2020; **11**: 1759.

19. Winthrop K, Vargas J, Drescher E *et al.* Evaluation of response to pneumococcal vaccination in patients with rheumatoid arthritis receiving upadacitinib: results from a phase 2 open-label extension study [abstract]. *Arthritis Rheumatol.* 2020; **72** (suppl 10). https://acrabstracts.org/abstract/evaluation-of-response-to-pneumococcal-vaccination-in-patients-with-rheumatoid-arthritis-receiving-upadacitinib-results-from-a-phase-2-open-label-extension-study/.

20. Brodmerkel C, Wadman E, Langley R *et al.* Immune response to pneumococcus and tetanus toxoid in patients with moderate-to-severe psoriasis following long-term ustekinumab use. *J. Drugs Dermatol.* 2013; **12**: 1122–9.

21. Chioato A, Noseda E, Stevens M *et al.* Treatment with interleukin-17A-blocking antibody secukinumab does not interfere with the efficacy of influenza and meningococcal vaccinations in health subjects: results of an open-label, parallel-group. Randomized Single-Centre Study. *Clin. Vaccine Immunol.* 2012; **19**: 1597–602.

22. Richi P, Martin M, de Ory F *et al.* Secukinumab does not impair the immunogenic response to the influenza vaccine in patients. *RMD Open* 2019; **5**: e001018.

23. Gomez E, Bishop J, Jack K *et al.* Response to tetanus and pneumococcal vaccination following administration of ixekizumab in healthy participants. *BioDrug* 2017; **31**: 545–54.

24. Blauvelt A, Simpson E, Tyring S *et al.* Dupilumab does not affect correlates of vaccine-induced immunity: a randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J. Am. Acad. Dermatol.* 2019; **80**: 158–67.e1.