

COVID-19 vaccination discussion – immune mediated neuromuscular diseases

Myasthenia gravis (MG) & Lambert-Eaton syndrome (LEMS), chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy, myositis, and Guillain Barre Syndrome (GBS)

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Top-line

1. COVID-19 if contracted is potentially fatal with many more seriously unwell in hospital.
2. The risk of hospitalisation and death with immune mediated neuromuscular diseases such as myasthenia gravis is probably higher than otherwise well people of a similar age.
3. The good news is that COVID-19 vaccines have already been shown to be dramatically effective in reducing hospitalisation by >90%.
4. Current COVID-19 vaccines have an excellent safety record including in patients with immunocompromised states, and with >100 million doses already given worldwide.

Purpose

This document is to distribute a discussion on COVID-19 vaccines for people with immune mediated neuromuscular conditions in Australia. The document is not a guideline nor medical advice. At present there is a dearth of high-quality data and this document is not intended to replace doctor-patient discussion and clinical judgment.

In places this document discusses some concerning aspects of COVID-19. While it is not the purpose of this document to be alarmist, it is important to understand this background to understand why the rapid development and rollout of vaccines has been necessary, and why vaccination has been recommended by the Australian government.

This document includes a lay section with FAQs, and a technical section, written in medical language and with references. Some patients may prefer to focus on the lay version, which is not so hard. The two are available together as some patients may wish to read both sections, some doctors may wish to have for consideration sample FAQs and answers, and having both together makes for easier distribution.

Lay summary (for patients)

COVID-19 caused by the SARS-CoV2 virus is a contagious global pandemic with very serious consequences. In *unvaccinated* people it frequently leads to hospitalisation, intensive care, and about 3% of people infected globally have died. This rate increases substantially with each additional decade of age past 60 and in people with other medical conditions.

Fatality rates of *unvaccinated* patients with myasthenia gravis are reportedly higher at 15, 19 & 30% in three studies, and at 10.5% in much larger numbers of patients with rheumatic diseases (including some patients with myositis) taking similar drugs to those used in myasthenia. While this could be an overestimation due to only the severe cases being reported, the apparent increased risk should at least be taken seriously. Fatality data for CIDP are not yet available.

Both the available vaccinations approved for use in Australia (Pfizer-BioNTech and AstraZeneca-Oxford) have been shown to dramatically reduce serious COVID-19 infection including hospitalisation by >90% in both the clinical trials and early real world studies in early-vaccinating countries such as Israel and Scotland. Fatality rates follow hospitalisation rates closely so we expect vaccination to have a similar reduction in deaths from COVID-19. This marked benefit already being seen with vaccinations internationally is very good news for patients at risk of serious COVID-19.

The vaccines have been demonstrated to be safe in large clinical trials and no additional serious concerns have arisen with now over 100 million doses having been administered in the USA, UK, Israel and other countries. Some short term side effects including a sore arm, headache, fatigue and even fever may well occur but these are generally far less serious than the infection itself. Vaccination for adults is recommended by the Australian department of health even for people without any medical condition, and Australian patients with a neuroimmunological condition such as myasthenia gravis should consider this advice even more carefully in the light of reported increased fatality risk of COVID-19 overseas.

Frequently asked questions (for patients)

Preamble: No vaccine is perfect, with complete protection against the infection and no side effects of the vaccine at all. A vaccine teaches our body's lymphocytes to defeat an infection before it is exposed, then when that exposure comes, the immune system is ready and better able to fight the infection.

All vaccines can hurt a bit, stimulate the immune system briefly, and may cause some short term side effects, such as a sore arm, headache, fatigue and fever. But these side effects are typically minor and insignificant compared with the impact of COVID-19. Being infected with the disease is a far higher risk - in addition to being fatal in some and needing intensive care in many more. The disease also has many complications in survivors including lung damage, strokes, and other serious short and long term side effects.

From the clinical trials and early real world experience, it is already clear that the risk of hospitalisation is dramatically reduced by vaccination.

Patients with immune mediated neuromuscular conditions have generally had many recommended vaccinations previously. The difference with COVID-19 is that the disease being prevented is new, but also more serious or more likely than most of the conditions people are already vaccinated against.

Should I have the COVID-19 vaccination?

Yes, the recommendation by the Australian government is well founded. The *unvaccinated* fatality (death rate) from COVID-19 in Australia is ~ 3.2% (28 Jan 2021). This means that on average, 3 out of every 100 people who contract COVID-19 do not survive and many more require treatment in intensive care or have long-term consequences. This is very high for a highly contagious illness which is likely to circulate through Australia once the border controls are open. In MG the situation is more alarming with fatality rate of 15%, 19% & 30% from the three largest studies – so 5-10 times the general population fatality rate, and the MG patients were younger. There may be several reasons for this, including the disease involving respiratory muscles and affecting breathing, the drugs used to treat MG, and the underlying immune issues associated with MG that can also inhibit responses to the SARS-COV2 virus that causes COVID-19.

Is the vaccine likely to cause GBS or contribute to neuropathy

To date, no cases of GBS have been associated with the COVID-19 vaccines in trials, and surveillance is ongoing. Some cases of GBS *have* been reported following COVID-19 infection. At this time, there is no reason that those who had GBS in the past should not receive the current COVID-19 vaccines.

See also: Foundation Global Medical Advisory Board statement on COVID vaccines for CIDP and MMN, January 21, 2021 (<https://www.gbs-cidp.org/2021/01/21/foundation-global-medical-advisory-board-statement-on-covid-vaccines-for-cidp-and-mmn/>)

See also: CDC statement: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/underlying-conditions.html#:~:text=Persons%20who%20have%20previously%20had,COVID%2D19%20vaccine%20clinical%20trials.>

Could the vaccine trigger a relapse of my condition?

It is theoretically possible, but less likely than infection with COVID-19 itself causing a relapse. All of the COVID-19 vaccines can produce side effects that include fever and fatigue. So an underlying neuromuscular condition may feel worse for the several days of these post vaccine symptoms, but it resolves quickly.

What if I am on treatment that is modifying or suppressing my immune system?

The available vaccines are considered to be safe in people who are immunosuppressed. None of the currently available vaccines are “live-attenuated virus” vaccines and do not pose any risk of causing the disease which they are aiming to prevent.

Will the vaccine still work if I am on treatment that is modifying or suppressing my immune system?

That is a very good question and one where knowledge is presently imperfect. Any level of vaccination is safer than not being vaccinated. Studies looking at this question for the COVID-19 vaccinations are currently being undertaken, including a study in Australia. Immunosuppressive treatments *can* reduce the effectiveness of vaccination to a variable degree, but it remains very worthwhile being vaccinated if you are on immunosuppressive therapy.

Generally people should be vaccinated as soon as the vaccine is available, but for certain cyclical treatments including IVIG, plasma exchange, rituximab and cyclophosphamide the timing of the vaccine and the treatment may require coordination.

Please discuss all these aspects with your treating doctor if they apply to you.

Should I stop, delay or hold off on starting my therapy until after I have been vaccinated?

It is not suggested that you suspend your therapy around the time of your vaccination unless advised to do so by your neurologist or other treating doctor. For those on intermittent therapies or who are just about to start a new therapy there may be some scope to better coordinate the timing of your therapy with any planned vaccination, but this should only be done in consultation with your treating doctor to ensure that the risks of any delay with your therapy will be minimal or can be reduced in some way.

The clinical trials and approval processes have been accelerated; how can I be sure that the vaccines are safe?

The very large clinical trials and approval processes used in Australia to assess the safety of medications and vaccines have been consistent with normal processes, they have simply been undertaken more rapidly than usual because of the urgency of the situation. The process of approval by the Therapeutic Goods Administration (TGA), which approves medications and vaccines in Australia, has been completed for both the Pfizer/BioNTech and AstraZeneca/Oxford vaccines. The TGA followed their usual procedures and will only approve a vaccine for COVID-19 once they are satisfied that it is safe. While some of the technology being used in the vaccines is new, this technology has been in development over many years and the process of testing the vaccines in pre-clinical studies and then clinical trials has been following standard procedures. The clinical trials for these vaccines have involved 10's of thousands of participants. In addition, now >100 million people have already been vaccinated worldwide and to date, no rare safety concerns have arisen.

Which vaccine would be best for me?

While there are some small differences in the efficacy and side effect profiles for each of the vaccines, all of the COVID-19 vaccines that are currently available are very effective and very safe. All the vaccines have shown that they dramatically reduce the risk of hospitalisation from COVID-19. You should therefore have the vaccine that is offered to you. This is likely to be determined by prioritisation and local availability, and it is unlikely there will be a choice.

What if I have had a previous allergic reaction to a vaccination?

You should advise the person administering the COVID-19 vaccine if you have ever had an allergic reaction to either an earlier dose of the COVID-19 vaccine or any other vaccination.

Patients with other kinds of allergies are safe to proceed to vaccination. Vaccination centres are fully prepared to manage allergic reactions if they were to occur. A major study has indicated a rate of allergic reactions is very low, at less than 5 cases per million doses.

Could I just wait until everyone else has been vaccinated and rely on “herd immunity” to protect me?

The sooner that as many people as possible are fully vaccinated against COVID-19 the safer we will all be. Relying on everyone else to be vaccinated to prevent you individually being exposed is unlikely to be an effective strategy. Leading Australian experts have stated that it is quite likely that COVID-19 infections may become a recurring phenomenon around the world and that outbreaks may occur from time to time. While being vaccinated does not eliminate the risk of contracting COVID-19 at an individual level, it does very significantly reduce the risk of getting severe disease and dying as a result of the infection. From a personal protection point of view, it is very important to be vaccinated. It is also likely that future travel, including international travel will be dependent on being able to prove that you have been vaccinated against COVID-19.

Technical section (for doctors)

Introduction

The current number one health priority around the world is rapid and efficient roll out of an effective vaccine to contain the COVID-19 pandemic. More than 100 million people have been infected and over 2.5 million have died worldwide (<https://coronavirus.jhu.edu/> doa25022021). Numerous factors known to increase the risk of complications and death from COVID-19 have been clearly defined (age over 60, obesity, diabetes, heart disease, lung disease, high blood pressure, pregnancy and certain ethnicities). A number of groups have been prioritized for early access to the vaccine, including older adults and younger adults with an underlying medical condition (<https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/getting-vaccinated-for-covid-19/when-will-i-get-a-covid-19-vaccine> doa25022021). Note “*People will need to provide proof of these conditions to demonstrate their eligibility for priority vaccination via My health record, a health professional referral if required or a declaration form.”

The fatality rate from COVID-19 in the *unvaccinated* population in Australia is consistent with other parts of the world at 3.2% (28 Jan 2021) primarily influenced by advanced age. The situation in people with myasthenia gravis is more concerning. Three studies show fatality rates of 30% (Brazil), 15% (France) and 19% (Global registry, mainly USA/UK) from >200 patients with mean ages in the 50s (¹⁻³ and data on file). There may be several reasons for this including: myasthenia affecting breathing, as does COVID-19; patients on immunosuppressive medications including prednis(ol)one; and other immunological abnormalities commonly associated with myasthenia, such as antibodies that prevent the desirable interferon response to viral infections⁴. No systematic outcome data is available for COVID-19 in patients with CIDP.

Related conditions requiring immunosuppression may give further guidance as to any real increase in COVID-19 risk. A reporting bias might be considered as an explanation for apparently high fatality rates with myasthenia gravis. Fatality rates do not appear to be generally increased in MS registries, with the possible exceptions of patients who have received corticosteroids such as IV methylprednisolone, ocrelizumab, and rituximab (⁵ and data on file). It would be expected that similar reporting and observation biases apply to MS and MG, suggesting that the higher fatality rate in MG should be considered seriously. Patients with rheumatic disease including some patients with myositis receive somewhat similar therapies to MG patients including in combination. In a global rheumatic diseases registry of >3000 COVID-19 cases, 10.5% died⁶. In this case drugs of concern in logistic regression analysis were corticosteroids particularly prednis(ol)one doses >10mg daily (Odds ratio OR 1.69), immunosuppressants grouped (OR 2.22) and rituximab (OR 4.04).

So far, there does not appear to be an overall increase in GBS or CIDP following SARS-COV2 infection or vaccinations, although there have been cases of GBS reported in association with COVID-19 infections. A UK based epidemiological study has found no causal association between COVID-19 and GBS⁷. This means that GBS developing at the same time or close to that of COVID-19 is most likely coincidental. Patients with prior GBS are often concerned about any future vaccination, but with rare exceptions, recurrence of GBS is unusual. GBS is a medical event of special interest for reporting for vaccines. In the last 40 years there has not been an increase in GBS associated with influenza vaccines, and GBS has been associated with influenza infection but not vaccination in controlled year on year studies⁸.

Vaccines

Three vaccines are being proposed for distribution to Australians from mid-February 2021. These are the Pfizer/BioNTech vaccine (20M doses, 2 doses 3 weeks apart), the AstraZeneca/Oxford vaccine (53.8M doses, 2 doses 4-12 weeks apart) and the Novavax vaccine (51M doses, 2 doses, awaiting TGA approval).

Note also the Australasian Society for Clinical Immunology and Allergy document on vaccination including in people with allergic conditions:

https://www.allergy.org.au/images/stories/pospapers/ASCIA_HP_Position_Statement_COVID-19_Vaccination_2021-03-02.pdf

mRNA vaccines (Pfizer/BioNTech – “Comirnaty”)

These vaccines use modified RNA spike protein of the SARS-CoV-2 virus in a lipid nanoparticle that is taken up by relevant antigen presenting cells. This in turn triggers an immunological reaction against the spike protein thereby conferring immunity. This is a new mechanism for vaccination. The Pfizer vaccine was found to be safe and 90 - 95% effective in a large phase III, placebo-controlled, clinical trial. The Pfizer/BioNTech vaccine has been approved for use in Australia by the TGA with a 2nd dose interval of at least 3 weeks. It was the first COVID-19 vaccine to be rolled out in February 2021 and currently requires -70C storage.

DNA/viral vector vaccines (AstraZeneca – “ChAdOx1-S” [Oxford])

This vaccine uses the spike protein corresponding DNA sequence that has been inserted into a simian adenovirus (common cold virus) vector that is able to result in effective antigen presentation but not replication in humans. The AstraZeneca vaccine was found to be safe and 60- 90% effective in a large phase III, placebo-controlled, clinical trial. Effectiveness on both clinical and immunological (neutralizing antibody geometric mean titres) was more effective with a longer interdose interval of 12 weeks. The AstraZeneca/Oxford vaccine has been approved by the TGA with a 2nd dose interval of 4-12 weeks. It is being rolled out in the coming months in Australia and requires refrigerated storage, which is routine for vaccines.

Protein vaccines (Novavax – “NVX-CoV2373”)

These vaccines use the spike protein or a part of the protein together with an “adjuvant” that stimulates the body’s immune system. Data for the Novavax vaccine have been released indicating an efficacy of 89.3%. No safety data are available yet for the phase 3 studies but there were no significant concerns in the phase 2 study including in Australian patients. The Novavax vaccine is expected to be made available in Australia later in the first half of 2021.

Specific therapies

Different immune therapies may affect the severity of COVID-19 infections, if contracted⁹. Some immune therapies also influence vaccine effectiveness as measured by humoral (antibody)

responses, including anti-CD20 monoclonal antibodies. Cyclical drugs used in neuroimmunology patients may require risk and timing assessments with respect to vaccination, and possible short term suspension of therapies. This particularly includes lymphocyte ablative therapies. Assessment of humoral responses after vaccination examining spike protein antibodies is available and could be considered when an impaired vaccination response is anticipated in selected patients. Given the paucity of specific data for neuromuscular diseases, some data from rheumatic diseases is included.

Corticosteroids – predniso(lo)ne, methylprednisolone, dexamethasone

Prednisolone and other corticosteroids may increase the risk of serious infections and death generally, especially in higher doses¹⁰. They may also increase the risk of severe or fatal COVID-19, including when given as IVMP¹¹, or as daily prednis(ol)one $\geq 10\text{mg/d}$ relative to other agents in rheumatic diseases⁶. Response to vaccines may be reduced but generally studies have been done on patients taking multiple therapies and positive responses to neoantigen vaccines such as Hepatitis B still occur in most patients¹².

Dexamethasone is used as a treatment to reduce the fatality rate from Acute Respiratory Distress Syndrome (ARDS) response once COVID-19 has reached critical care level, but this is a different context¹³.

Antiproliferatives – azathioprine, methotrexate, leflunomide, mycophenolate

In a rheumatic diseases and COVID-19 series methotrexate (MTX) was the reference medication (given a relative risk of 1) noting that the overall death rate was 10.5%⁶. In that study antiproliferatives were grouped with other drugs as “Immunosuppressants (except glucocorticoids)” with a relative to MTX increased risk of death with COVID-19 of 2.22. However in that study the mycophenolate and azathioprine group also included cyclophosphamide, cyclosporine and tacrolimus which have different mechanisms of action. Leflunomide had a relative risk of 1.56. Data from teriflunomide monotherapy studies showed only modest quantitative and qualitative reductions in vaccine responses, with no significant effect on protective effectiveness¹⁴.

CD20 (B-cell) drugs – e.g., rituximab

Rituximab is one of the many drugs not officially indicated for the treatment of neuroimmunological conditions that nonetheless is a very important treatment in widespread use.

Rituximab has been associated with an increased rate of COVID-19 death (OR 4.04x) in an observational study in rheumatic diseases⁶. Italian registry data early in the pandemic suggested an increase in hospitalisation with CD20 mabs in MS¹¹. US data is awaited. Roche / Genentech data showed a 5.5% fatality rate for ocrelizumab treated MS patients⁵.

Anti-CD20 monoclonal antibodies significantly impair the response to primary/neoantigens in different contexts including rituximab and a bacteriophage¹⁵, rituximab and hepatitis A¹⁶, ocrelizumab and KLH¹⁷, and rituximab and KLH¹⁸. It is important to consider the time point of vaccination in trajectory to the time point of B-cell depletion versus B-cell repopulation. The largest RCT focused on vaccinating patients on rituximab 32 weeks after the last rituximab course when some return of B-cells might be expected and achieved a detectable humoral response to KLH of 47% (RTX / MTX) vs 93% (MTX alone)¹⁸.

What to do about patients requiring COVID-19 vaccination and off-label rituximab / CD20 mab long cycle therapy is complicated. In Australia at the time of writing we have the comparative luxury of

very low rates of community acquired COVID-19. Options that some treating doctors may be considering include:

- Vaccinate patients on rituximab as soon as the vaccine is available no matter when in the rituximab cycle.
- Vaccinate patients as late as possible in the rituximab cycle but not so close to the next standard infusion time that the vaccine response is ablated, for instance in a 6th monthly rituximab cycle give the vaccine doses at 4 & 5 months.
- In patients where the underlying neuroimmunological disease can permit some delay in the next rituximab cycle or alternative therapies, delay vaccination to 7-8 months after last dose when RCT evidence suggests a vaccine response is reasonably likely, again with a month between last vaccine dose and next rituximab dose.
- Any of the above plus check post vaccination serology and if negative re-vaccinate with a booster dose, possibly with a rituximab delay or alternative therapy.

Cyclophosphamide

COVID-19 fatality rates are higher in patients receiving chemotherapy and it is plausible that this applies to cyclophosphamide as immunotherapy, caution might be exercised in the absence of data. Vaccine response rates may also be substantially impaired and vaccination including timing requires special consideration.

TNF inhibitors

TNF inhibitors have not been associated with an increased risk of hospitalisation in a rheumatic diseases population and there may be a trend to decreased risk. Vaccine responsiveness on TNF inhibitors to Hepatitis B may be mildly attenuated in an inflammatory bowel disease population¹².

IVIG & plasma exchange

These therapies are unlikely to affect COVID-19 severity. ASCIA suggests not vaccinating around the day of the procedure to avoid confusion over any possible side effects (<https://www.allergy.org.au/hp/papers/guide-immunodeficiency-autoimmunity-and-covid-19-vaccination>). At present IVIG does not contain high levels of SARS-COV2 antibodies and is therefore unlikely to offer protection from COVID-19.

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