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COVID-19 VACCINATION IN PATIENTS WITH GASTROINTESTINAL AND LIVER DISORDERS

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Introduction

As COVID-19 vaccination is rolled out across Australia, it will soon be our patients' turn to make a choice - to be vaccinated or not. What can Gastroenterologists advise? The following is a brief overview based on current information and recommendations from international liver and gastroenterology organisations including the AASLD, EASL, ILTS, BSG, ECCO and IOIBD.

First, there is publicly available information on frequently asked questions about Covid vaccines from the Australian Government Department of Health that we should point our patients towards to make sure the information they receive is consistent with the Australian national strategy.

Second, we should provide advice to our patients with underlying gastrointestinal (GI) and liver conditions including chronic liver disease (CLD), inflammatory bowel disease (IBD), and those treated with biologic agents, immunosuppressants and anti-rejection drugs.

Two vaccines (Pfizer/BioNTech COVID-19 vaccine (Comirnaty) and AstraZeneca COVID-19 vaccine) have received provisional approval by the Therapeutic Goods Administration (TGA). It is anticipated that additional vaccines will receive approval in the future.

What are the potential concerns for our patients?

As expected for any new vaccine, patients and clinicians may have concerns around side effects, safety (in the context of underlying disease and comorbidities), efficacy (particularly in the setting of immunosuppression) and whether one vaccine might be preferred over another.

In April 2021, Australian cases of suspected thrombosis with thrombocytopenia syndrome (TTS) (also called Vaccine Induced Prothrombotic Immune Thrombocytopenia (VIPIT)) following vaccination with AstraZeneca COVID-19 vaccine were reported to the TGA. The cases were similar to those published from Norway and Austria in the New England Journal of Medicine in April 2021. The majority of cases are in patients under 50 years of age.

Safety

Both the Pfizer/BioNTech Comirnaty and the AstraZeneca COVID-19 vaccines have been approved by the TGA after rigorous assessment of safety and efficacy data. In addition, nearly 200 million people have been vaccinated around the world and the adverse events profile of the vaccines are as predicted by the clinical trials. There is so far limited specific information on safety or efficacy in patients with underlying GI or liver disease, or in those who are immunocompromised or receiving immunosuppressant therapy. However, no particular

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concerns are anticipated. Large international registries are tracking safety in these populations and have thus far reported no increased risk of adverse events.

Vaccination should be deferred in those suffering from acute severe febrile illness or acute infection. Adverse reactions commonly reported with both vaccines, include headache, arthralgia, myalgia, injection site pain and swelling, fatigue, chills, and pyrexia. Specific rates of adverse reactions are provided in the approved product information.

Within the limitations of existing data, vaccinations do not appear to be associated with flares of activity of immune-related disease or transplant rejection. Irrespective of underlying immune-related disease or transplantation, patients should receive COVID-19 vaccination and disease activity should not impact the timing of vaccination or the choice of vaccine.

There are specific considerations around COVID-19 vaccination in pregnancy and breastfeeding. Guidance provided by the Australian Department of Health will be updated as new vaccines are granted approval. There are currently limited data regarding safety of COVID-19 vaccines in pregnant women. Preliminary findings of safety of mRNA vaccines in pregnancy did not show any obvious safety concerns although more follow-up is awaited. The vaccines are recommended in breastfeeding women.

The Pfizer Comirnaty vaccine has received provisional approval for administration to individuals ≥ 16 years, and the AstraZeneca vaccine is approved only for adults aged ≥ 18 years. Safety and efficacy have not been established in younger people, however it is likely that approvals will be extended as more data emerge. A preliminary study of more than two thousand 12-15 years old adolescents the Pfizer Comirnaty vaccine demonstrated 100% efficacy and was well tolerated.

Since the emergence of Australian cases of confirmed TTS with the AstraZeneca vaccine, the Australian Technical Advisory Group on Immunisation (ATAGI) has recommended that the Pfizer Comirnaty mRNA vaccine is preferred in people under the age of 50 years. The majority of cases of TTS have occurred in patients under the age of 50 with a rate of TTS estimated to be about 6 cases per million vaccinated. It occurs around 4-26 days after vaccination and almost all have occurred after the first dose. The AstraZeneca vaccine can be given to adults under 50 years where the risk of COVID-19 infection outweighs the risk of the vaccine and should be given to those who have already had their first dose without any serious side effects. Otherwise, as there are currently very few cases of community transmission of COVID-19 in Australia, it is reasonable to recommend that patients under the age of 50 years with underlying chronic GI or liver disease, who are immunosuppressed or have comorbidities wait until they have access to Pfizer Comirnaty vaccine. The risk factors for TTS have not been fully elucidated. The presence of baseline thrombocytopenia (eg. related to portal hypertension) is not a risk factor for TTS. Patients with prior heparin induced thrombocytopenia (HIT) are likely at risk of TTS through a similar mechanism and should not receive AstraZeneca vaccine. It is currently felt that there is no evidence of a risk of thrombotic disease after COVID-19 vaccination in people with a history of clotting conditions. The Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) is providing regular updates of the evidence around risk factors, diagnosis and management of TTS.

Efficacy

It is important to recognise that the reported efficacy rates from large clinical trials refer to prevention against symptomatic SARS-CoV-2 infection. Both vaccines are highly effective at preventing symptomatic infection and in particular, severe COVID-19 infection. It is currently unclear as to how effective they are at preventing transmission and asymptomatic infection with SARS-CoV-2. Furthermore, as few patients with underlying severe

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liver disease, immunocompromise, liver transplantation or receiving immunosuppressant therapy were included in clinical trials, there are limited data regarding efficacy rates in these populations. It is known that efficacy with other (non-COVID-19) vaccinations is reduced in these populations however while there is a theoretical risk of sub-optimal vaccine response, it is still recommended that all patients receive vaccination regardless of comorbidity. Real-world data on vaccine responses in immunocompromised patients are anticipated.

Clinicians should advise patients over the age of 50 years to take whichever vaccine becomes available to them as all offer high protection against severe COVID-19 infection. Pfizer Comirnaty vaccine is recommended in patients under 50 years of age.

There have been recent concerns about efficacy of vaccines to prevent symptomatic infection with evolving COVID-19 variants, especially the faster spreading UK variant, B.1.1.7, and South African variant, B.1.351. This is a rapidly evolving field as more variants are being reported around the world.
Many of the vaccines will be modified to adapt to emerging variants.

Effect of corticosteroids on effectiveness of vaccination

Corticosteroids have significant immunosuppressive effects and high dose steroids (20 mg of greater equivalent prednisolone dose) are associated with impaired antibody development in response to immunisation. Patients with IBD or autoimmune conditions frequently require relatively short duration of high dose steroids, which may impact vaccine efficacy. Depending on the rates of COVID-19 in the community, it may be reasonable to delay vaccination until patients have tapered down or ceased corticosteroids. Any decision on timing of vaccination should be after a discussion with the patient on the risks and benefits of any proposed delay.

Vaccination in patients on biologic therapy for IBD

There are no specific considerations regarding timing of vaccination and administration of biologics for treatment of IBD. Vaccination should not be delayed due to scheduled biologic dose. Furthermore, the scheduled dose of biologic medication should not be delayed because of vaccination. The second dose of vaccine should not be delayed in patients receiving biologics and must be administered to provide high level protection against COVID-19 infection. In a study of immunogenicity in patients receiving anti-TNF therapy, poor antibody responses were observed after a single vaccine dose but almost all patients achieved seroconversion after the second dose. It is very important that all patients who received the first dose of AstraZeneca or Pfizer Comirnaty vaccine receive their second dose of the same vaccine as scheduled.

Choice of vaccines

There are significant differences between the two vaccines that have so far received provisional approval. Clinical guidance on use of COVID-19 vaccines has been provided by ATAGI and it is recommended that this advice is viewed as regular updates are provided. Detailed information can be found in the approved Product Information for the Pfizer/BioNTech mRNA (Comirnaty™) vaccine and the AstraZeneca Adenovirus vector (ChAdOx1-S) vaccine. Consumer medicine information is available for the Pfizer Comirnaty vaccine and the AstraZeneca vaccine.

As neither is a live-attenuated or replication-competent vaccine, they cannot cause COVID-19 or any other viral infection which is something we should emphasise to our patients.

The Pfizer Comirnaty mRNA vaccine is delivered as 2 intramuscular injections 3 weeks apart. A phase II/III trial of Comirnaty is ongoing with >43,000 individuals aged ≥12 years enrolled. An interim analysis reported vaccine efficacy of 95% in preventing symptomatic laboratory-confirmed COVID-19 in people aged ≥ 16 years without

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evidence of prior infection with SARS-CoV-2. Similar high efficacy was observed in adults aged ≥ 65 years, and those with 1 or more medical comorbidity or obesity. It will be administered to those identified as the highest priority according to the national rollout phases and is now recommended in those under 50 years of age. It is more expensive to produce, store and distribute because of difficult logistics related to the requirement for freezing at temperatures of -90°C to -60°C and is not being produced in Australia.

The AstraZeneca viral vector vaccine, is recommended to be delivered as 2 intramuscular infections 12 weeks apart as efficacy is greatest at this dosing interval. Phase II/III trials of COVID-19 Vaccine AstraZeneca are ongoing with >57,000 individuals aged ≥18 years enrolled. Overall vaccine efficacy was 70.4% in preventing symptomatic laboratory-confirmed COVID-19, in people aged ≥18 years 15 or more days after the second dose in the primary efficacy study population. Reported vaccine efficacy rates vary as data are updated. Vaccine efficacy varies with dose interval. When the two doses are given ≥12 weeks apart, vaccine efficacy for prevention of symptomatic laboratory-confirmed COVID-19 was 82.4%. While data are so far limited in those aged ≥65 years, data from a large phase III clinical trial is expected in late March 2021. While initially it will be imported, this vaccine will be produced in Australia in the future and can be stored and transported at normal refrigeration temperatures (2°C to 8°C). It is the vaccine that is likely to be offered to people over the age of 50 years in the general community as recommended by ATAGI.

Summary

People with chronic liver disease, IBD and post-transplant are particularly vulnerable to severe illness with COVID-19 with higher morbidity and mortality. Hence, we should encourage our patients to be vaccinated as early as the vaccine is available to them, to protect against severe COVID-19 infection if they were to be exposed. While the proportion of people with these chronic conditions in Phase 3 clinical trials of vaccines is small emerging real-world data is very reassuring. There is no reason at this stage to be concerned about the efficacy or safety of either vaccine for our patients, although since emergence of cases of TTS, Pfizer Comirnaty vaccine is recommended in those under 50 years. There is no reason to withhold vaccination due to concerns about immunosuppression. As for efficacy, questions remain about how effective the vaccines would be in stimulating immunity in those with chronic disease or immunocompromise. Despite these gaps in data to date, the vaccines appear to be very safe and effective in preventing symptomatic COVID-19 infection and we should urge all our patients to be vaccinated. As vaccines may not prevent transmission of infection, the use of masks, social distancing and hand hygiene will continue to be recommended for some time.

We recommend that GESA members encourage their patients to take up COVID-19 vaccination when it becomes available to them. Patients and clinicians should keep themselves up-to-date with evolving knowledge in this field and follow recommendations from the Australian Government Department of Health. We await real-world data regarding the efficacy and safety of COVID-19 vaccination in our vulnerable patients with GI and liver disease.

Disclaimer

The Gastroenterological Society of Australia (GESA) provides the above advice to guide gastroenterologists and hepatologists who provide care for patients with chronic liver diseases, transplant recipients and IBD during the COVID-19 pandemic. This advice should be modified to fit the context of individual medical practice based on the local policies of the relevant health facilities. Given the rapidly evolving situation, this advice is subject to change and we will make efforts to update them as needed. Please check the Australian Government website for the latest information on COVID-19 vaccines.