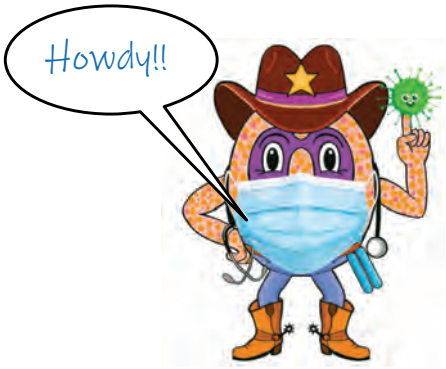

DR SPUR'S MYSTERY CASE

Living with an antibody deficiency during the COVID-19 pandemic

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Dr P Balule
General Practitioner

Dear Dr Spur

A 34-year-old nurse working in my practice was diagnosed with common variable immunodeficiency (CVID) six years ago. Her IgA and IgG levels were well below 2 SD for her age and she had absent vaccine responses to polysaccharides after a vaccine challenge with Pneumovax 23®. She has been on IV immunoglobulin replacement (IRT) ever since and her condition has improved remarkably. Before IRT was initiated, she had recurrent episodes of sinusitis and at least two pulmonary infections each year. She developed mild bronchiectasis, which has subsequently stabilised on Chest CT. She has an eight-year-old son, who has been diagnosed with symptomatic selective IgA deficiency. He has been well on Azithromycin prophylaxis.

Could you please advise me on the following questions?

- Would my nurse and her son be susceptible to more severe COVID-19 disease?
- Should she be vaccinated against COVID-19, bearing in mind that she had absent specific antibody response to polysaccharides?
- If COVID-19 vaccination is indicated, when is the ideal time after her last dose of IV IRT, prior to administering the vaccine?
- Is IRT protective against COVID-19 infection?
- Are PID patients prolonged carriers of SARS-CoV2?

Your advice is always highly appreciated.
Kind regards
Dr Balule

Dear Dr Balule

Thank you for your relevant questions at a time in which we are still battling the SARS-CoV-2 virus in the ever-evolving SARS-CoV-2 pandemic. As time passes, we continue to gain additional insights into how patients with antibody deficiencies and other inborn errors of immunity (IEI) are affected. Interestingly enough, we gain much insight into the immune responses crucial to the pathophysiology of COVID-19 disease by studying abnormalities in patients with IEI. This can guide scientists in developing treatment and help identify patients who may be at an increased risk for severe disease.

My answers to your questions in numerical order:

1. At the start of the pandemic, it was assumed that patients with primary immunodeficiency (PID) would be more susceptible to severe COVID-19 disease. I don't know all the answers, but can share with you what I have gleaned from the available literature. To date, two retrospective survey studies (Meyts et al; Shields et al) reported fewer PID patients with severe COVID-19 than initially suspected. However, the data may have been confounded by the relative rarity of patients with PID and due to strict precautionary measures instituted by this population early on in the pandemic. Another study conducted by a Japanese group found a positive correlation between the frequency of selective IgA deficiency and the COVID-19 infection rate in their population. From other available literature, mild and asymptomatic COVID-19 infections are often observed in patients with antibody deficiencies. The same comorbid risk factors present in the general population, including older age, predispose patients with PID to severe COVID-19 infection. Patients with sub-therapeutic IgG levels on IRT are also at increased risk of developing more severe disease.

   It is now emerging that patients with impaired signalling of type 1 interferon may be at risk for more severe COVID-19 disease. Inborn genetic errors in crucial type-I IFN pathway genes and autoreactive antibodies that block IFN responses have been significantly associated with life-threatening COVID-19 pneumonia. These patients should therefore take additional precautions. Patients with CVID often have associated autoimmunity, and it can be hypothesised that the presence or absence of type-I IFN autoantibodies can predispose patients with CVID to severe or life-threatening SARS-CoV-2 infection.

2. SARS-CoV-2 vaccine responses in patients with antibody deficiencies may be blunted; however, it is recommended that patients with PID and secondary immunodeficiencies receive COVID-19 vaccinations. The rationale behind the recommendation of vaccination is that, even with absent antibody responses, T-cell responses may be generated. This has been observed after the use of many viral vaccines, including influenza vaccines, which are also recommended

for use in PID patients. The SARS-CoV-2 vaccines currently approved for use or in clinical trials in South Africa are either mRNA, protein sub-unit or replication-deficient vector vaccines. None of these vaccines is live-attenuated. Should they become available in the future, live-attenuated vaccines should not be administered to those patients with PID who have a contraindication for live vaccines.

3. If a patient is receiving IV IRT, it is recommended that the vaccine be given two weeks after the last immunoglobulin infusion to minimise the chance of side-effects and also to give the vaccine the maximum chance to work. If infusions are administered at intervals less than every four weeks, or subcutaneous IRT is used, it is suggested that patients have the vaccine mid-way between two consecutive administrations.
4. Current immunoglobulin products have been collected prior to the pandemic. They do not demonstrate neutralising antibodies to SARS-CoV-2 and should therefore not be considered to confer any protection. This may be expected to change in the next year or two.
5. Data are emerging that patients with PID may remain PCR positive for SARS-CoV-2 and may shed the virus, with or without symptoms, for longer periods than immunocompetent individuals. There is not yet sufficient evidence on the infectiousness of these viruses; however, there have been some anecdotal reports of prolonged viral shedding. The current South African testing guidelines do not make provision for follow-up testing after the patient becomes asymptomatic and has fulfilled the prescribed isolation recommendations. However, should a patient with a known PID remain symptomatic, I suggest that you liaise with a clinical virologist or the National Institute for Communicable Diseases (NICD) to discuss follow-up testing.

Dr Spur's take-home message:

In conclusion, with regard to your patient with CVID, it is important for her to maintain therapeutic IgG levels.

The whole family should be encouraged to adhere to strict handwashing, mask-wearing and social distancing protocols.

Even though a blunted antibody response can be expected, SARS-CoV-2 vaccination is still advised, as is the case with annual influenza vaccination. A T-cell response is likely to confer some protection.

SARS-CoV-2 vaccination should preferably be administered mid-way between two consecutive IRT doses.

All adult members of her family should ideally be vaccinated in order to obtain herd immunity within the family.

The family should adhere to local guidance from the South African Department of Health and NICD.

Dr Spur's mystery SOLVED:

'Everything about COVID-19 is still a mystery'

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