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|  | Question | Answer |
| 1 | Is there evidence to support convalescent plasma over monoclonal antibodies in the treatment of patient with antibody deficiency? | Currently there is no evidence directly comparing any antibody based treatment (monoclonal antibodies, convalescent plasma or hyperimmune globulin) in the treatment of patients with antibody deficiency.  The potential advantage of monoclonal antibodies are that the pharmacokinetics of the drug, in particular the dose and neutralising capacity are better understood, so treatment efficacy or failure can more easily be attributable to the antibody component of the product.  This has to be balanced against the mounting evidence that any antibody based treatment can support viral clearance in antibody deficient patients, and accessibility to such treatments in different health care setting. |
| 2 | Should dosing of replacement immunoglobulin change if a patient is receiving an antibody based treatment for COVID-19 | No. The consensus of the panel was not to adjust the dosing or frequency of conventional immunoglobulin replacement therapy (intravenous or subcutaneous) if the patient was receiving an antibody based treatment for COVID-19. |
| 3 | What are the recommendations regarding COVID vaccination for patients with antibody deficiency.  Do you have any insight into vaccine efficacy in this cohort? | The consensus of the panel was that patients with antibody deficiency should be vaccinated as soon as possible against COVID-19. At present, there is no data supporting the use of any particular vaccine in patients with antibody deficiency, although a number of national and international studies are exploring this important question.  Early data suggests that vaccine responses in patients with antibody deficiency are highly variable and studies are exploring the reasons for this. No data exists so far for whether T-cell responses in the absence of antibody responses will provide benefit. |
| 4 | How long do serological tests remain positive following the administration of antibody based therapeutics and when can one be that serological results indicate active immunity in the patient? | Our experience suggests serology is only transiently positive following the administration of convalescent plasma. Following the administration of 2 units of plasma to a patient with secondary B cell aplasia, neutralising anti-spike IgG antibodies were detectable at 1 week post infusion. At 3 weeks post infusion, antibodies remained weakly detectable, but they were no longer neutralising. (McKemey et al, J Clin Immunol  2021 Feb 20;1-4). With REGN-COV-2, effective neutralisation has been at 4 weeks post administration (Lowe DM – *unpublished observations*).  Our opinion is that the persistence of seropositivity beyond three months would favour the individual making their own response; however, antibodies will gradually emerge in regular IVIG/SCIG products, confounding this in the future. |
| 5 | What do you think about early inhaled budesonide as a treatment for COVID-19? | Early data from the STOIC trial (Ramakrishnan et al, Lancet Respiratory Medicine April 09, 2020) and the press release from the PRINCIPLE study suggest that budesonide is a promising candidate drug which may prevent disease progression in healthy individuals with mild COVID-19. To some extent, this is concordant with the observed efficacy of dexamethasone in hospitalised patients with severe COVID-19.  However, both the STOIC and PRINCIPLE trials were relatively small and open label; further studies are needed to confirm these promising early results. Furthermore, it is not clear whether these data generalise to those with antibody deficiency and, therefore, there is currently no recommendation for this treatment. |
| 6 | What would be the importance of measuring autoantibodies? Would there be a point to follow this to start early treatment? | This is a good question, and we recommend joining the ESID Grand Round in May which will deal with this issue, among others:  ‘Managing COVID in patients with Type 1 IFN pathway defects’  Date: Tuesday 18th May  Time: 17:30-18:30 CET |
| 7 | Do the kinetics of infections and the immune response against SARS-CoV-2 differ between children and adults with immune deficiency? | How the kinetics of infection and immune responses against SARS-CoV-2 differ between children and adults and between different immune deficiencies is not understood.  Risk factors for more severe outcomes include increasing age, the presence of comorbidities, particularly chronic lung disease and pre-existing lymphopoenia.  Further studies are examining the correlates of virological clearance in different immune deficiency populations. |
| 8 | What is the experience of treating patients prophylactically with antibody based therapeutics? | There are ongoing trials of using monoclonal antibody as very early treatments and prophylaxis against SARS-CoV-2 infection.  Data from the convalescent plasma arm of the UK RECOVERY trial (Horby et al - /doi.org/10.1101/2021.03.09.2125273) demonstrated non-significant trends towards clinical benefit in hospitalised individuals treated early with plasma, and those who were antibody negative when treated, suggesting this may be a promising approach for antibody deficient patients.  The panel was in favour of antibody therapy at an early stage for patients with antibody deficiency although access to treatment is currently a barrier. The panel have no experience with prophylactic use of antibody-based treatment in patients with antibody deficiency although agree that this is an important area for gathering data and future research. |
| 9 | What about emergent mutants in just 1 patient? Have you addressed this question? | Detailed case reports have demonstrated intra-host evolution of SARS-CoV-2 in antibody deficient patients (e.g. Kemp et al Nature (2021) 592, 277-282, Choi et al, NEJM 2020; 383:2291-2293). It has been hypothesised that antibody based treatments, in particular, convalescent plasma, could favour the selection of viral variants that may be less susceptible to neutralisation).  These reports are certainly concerning, and would favour the use antibody based treatments where the dose and pharmacokinetics can be more easily studied  Equally, the generation of viral variants may be prevented through the early treatment of infection in vulnerable groups with combination treatments that suppress viral replication (e.g. remdesivir) and facilitate viral clearance (e.g. antibodies).  The panel’s view is that they would not withhold antibody treatment based on concerns about mutation but would recommend serial viral sequencing after antibody therapy to gather more robust data in this area. |
| 10 | Many thanks for an excellent webinar. How do you think decisions on treatment and need for treatment is likely to change when those on IG replacement have significant COVID-19 antibodies on board giving initial COVID-19 protection? Do you think you may be more likely to treat in infection in this situation? | Evidence is conflicting regarding whether immunoglobulin products contained cross-reactive antibodies against SARS-CoV-2 prior to the pandemic (Schwaiger et al (2020), J Infect Dis 222(12), p1960, Ahn et al, J Allergy Clin Immunol 2021 Mar;147(3):876-877 ). Immunodeficient patients receiving immunoglobulin did not appear to have protection from hospitalisation or severe outcome in the UK study (Shields et al, J Allergy Clin Immunol 2021 Mar;147(3):870-87)  However, antibodies are emerging in products synthesised during the pandemic (Romero et al, Lancet Infectious Disease, February 16th 2021) and as vaccination programme continue, the percentage of seropositive donors will increase.  Further studies will be necessary to define the levels of antibody necessary to provide passive immunity in plasma products now, and in the future should viral variants emerge. In the short-term, these factors would not affect treatment decisions. |
| 11 | Is there evidence that antibody deficient patients drive mutations for other viruses? | There is an absence of evidence with respect to whether the immune responses in individuals with primary or secondary immune deficiency facilitate the emergence of viral variants.  There is some evidence that treatment with antivirals selects for certain variants (e.g. Ruis et al NEJM Nov 29;379(22):2173-2176) and further studies continue in this area. |