Response to Aviv et al.

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We read with great interest the correspondence by Aviv et al. [1] where the authors comment on our brief report describing a patient with chronic lymphatic leukemia with persistent COVID-19, who had marked improvement on treatment with remdesivir, but relapse after discontinuation of treatment. This pattern that was repeated after a second 10-day course of remdesivir [2].

Aviv et al. report a case of a 50-year-old female treated with rituximab for rheumatoid arthritis who also had prolonged COVID-19 but responded to treatment combining remdesivir and convalescent plasma (CP). The authors argue for the use of CP in B-cell depleted patients with prolonged symptoms of COVID-19.

Case reports and case series of B-cell depleted patients with persistent COVID-19 are accumulating. In addition to the article cited by Aviv et al., there have been other case series of patients with B-cell depletion, who responded well to CP [3-4]. However, there may be publication bias in thesereports, and cases treated unsuccessfully with CP are unlikely to be reported.

In our center we have treated ten B-cell depleted patients with prolonged COVID-19 (persistent symptoms and at least two positive SARS-CoV-2 PCR tests more than 50 days apart) with CP. Two of the patients were subsequently treated with monoclonal antibodies against the SARS-CoV-2 spike protein (mAb's), casirivimab/imdevimab. Only three of the patients treated with CP responded favorably, two patients had a temporary response, but later progressed and needed mechanical ventilation. Two of the ten patients died. Both patients treated with mAb's improved a few days after treatment and were discharged from hospital. mAb's have only recently become available in Denmark and access is very limited.

CP is an unstandardized product with an unstandardized dose. Even when only SARS-CoV-2 high-titer plasma is administered, the amount of neutralizing antibodies in the plasma pool is usually unknown. This variation in content increases the variability and unpredictability of treatment responses.

There are no randomized trials studying CP, hyperimmune immunoglobulin or mAb's in immunocompromised patients, and the evidence for efficacy of CP for the treatment of COVID-19 is scarce. Only one small randomized controlled trial from Argentina has shown clinical efficacy of CP among older adults treated early in the disease course [5]. The trial included 160 patients and showed a relative risk of severe respiratory disease of 0.52 for patients treated with CP vs placebo. The 95% confidence interval was wide, 0.29 to 0.94.

Larger trials have studied efficacy and safety of mAb's. The phase 3 Blaze 1 trial randomized 1,035 high risk outpatients, with a mean duration of symptoms of 4 days, to bamlanivimab/etesevimab or placebo [6]. Patients receiving the monoclonal antibody cocktail had a 70% reduction in risk of hospitalization or all-cause mortality by day 29. In another placebo controlled randomized trial, which included 275 adults with a median age of 44 years and a median duration of symptoms of 3 days, casirivimab/imdevimab reduced the risk of a medically attended visits [7]. The effect was largest among study participants who were antibody negative at baseline (6% versus 15% for the active arm compared to placebo). In the subgroup who were seronegative at baseline, the mAb's caused a faster decline in viral load.

Adverse reactions to CP are uncommon, but viral escape and selection of variants with mutations that render the virus resistant to CP and potentially also to antibodies induced by COVID-19 vaccines has been documented in severely immunocompromised patients treated with CP [8]. It is likely that mAb treatment of patients with impaired immune response and uncontrolled viral replication could result in a similar selective pressure and resistance development. The absolute risk of this adverse effect is currently not known.

Patients with B-cell malignancies and patients who have received anti-CD20 antibody therapy within the last year have a poor response to COVID-19 vaccination [9], further emphasizing the rationale for passive immunization strategies upon SARS-CoV-2 infection or exposure in these patients.

We believe that anti-SARS-CoV-2 antibody therapy of B-cell depleted patients may improve outcomes, especially if treatment is initiated early after exposure/transmission. Standardized products that have proven safe and efficacious in large randomized trials should be used, if available. It remains to be determined if combination therapy with antiviral drugs could reduce risk of viral escape and development of variants resistant to neutralizing antibodies.

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