



## COVID-19: Convalescent plasma as a potential therapy

**To the Editor:** SARS-CoV-2, the cause of COVID-19, has posed a significant threat to global health. No specific treatment or effective prophylaxis has been established, and care of severely ill patients is largely supportive, with poor outcomes in those requiring ICU admission. Experimental therapies include antiviral agents such as remdesivir,<sup>[1]</sup> lopinavir/ritonavir<sup>[2]</sup> and favipiravir,<sup>[3]</sup> hydroxychloroquine/chloroquine,<sup>[4]</sup> interleukin-6 inhibitors such as tocilizumab,<sup>[5]</sup> siltuximab<sup>[6]</sup> and sarilumab,<sup>[7]</sup> and COVID-19 convalescent plasma (CCP).<sup>[8]</sup>

CCP has been included in the treatment guidelines for severe COVID-19 in China,<sup>[9]</sup> and the Food and Drug Administration has recently approved its use for critically ill COVID-19 patients in the context of clinical trials and through the expanded access programme in the USA.<sup>[10]</sup> Interest has been expressed in the use of CCP for COVID-19 treatment in South Africa (SA).

CCP refers to plasma collected from donors who have recovered from COVID-19 and are likely to have produced neutralising antibodies to SARS-CoV-2. It is hypothesised that the infusion of plasma with virus-specific antibodies confers immediate transfer of passive immunity to the recipient and may improve the clinical course and outcomes by accelerating viral clearance and antibody-dependent cell-mediated cytotoxicity of infected cells.<sup>[11]</sup>

The use of convalescent plasma (CP) as passive immunisation to treat viral infections is not novel.<sup>[12]</sup> Early administration of CP has proved successful in reducing mortality from severe influenza<sup>[13,14]</sup> as well as the related epidemic coronavirus severe acute respiratory syndrome (SARS)-CoV,<sup>[15]</sup> and has been used successfully in Middle East respiratory syndrome (MERS)-CoV<sup>[16]</sup> and Ebola virus disease.<sup>[17]</sup> Studies using CP in various viral infections have shown improvement of both laboratory and clinical parameters,<sup>[13,18-22]</sup> including a reduction in the hyperinflammatory cytokine response, which appears to be a critical driver of morbidity and mortality in COVID-19.<sup>[23,24]</sup> Where CP was used to treat SARS-CoV infections, the absolute risk reduction in mortality ranged between 7% and 23%,<sup>[25-30]</sup> and CP was associated with earlier discharge from hospital.<sup>[15,26,27,30]</sup> It is because of the positive results of these trials, in addition to the lack of successful treatment options available at present, that the use of CCP has been considered in the current SARS-CoV-2 pandemic.

Studies of the use of CCP from China have shown potential benefit, including improved survival,<sup>[31,32]</sup> reductions in viral load<sup>[31-33]</sup> and improved radiological features.<sup>[31,32,34]</sup> These studies have various limitations, including small numbers of patients, lack of blinded, randomised or placebo-controlled trials, and patients receiving a multitude of different therapies. One study involving 6 critically ill patients<sup>[33]</sup> found that although all the patients became SARS-CoV-2 RNA-negative within 3 days of CCP infusion, 5 eventually died. Consequently, before CCP can be considered as an effective treatment option, testing of its safety and efficacy in large randomised controlled trials has been recommended,<sup>[8,35]</sup> and trials are underway in the USA, the UK, Canada, Brazil and Italy, as well as several other European countries. Early safety<sup>[36]</sup> and treatment<sup>[37]</sup> outcomes appear encouraging, with non-ventilated patients benefiting more than those requiring ventilation. Historical use of CP has shown that it is most effective when used as prophylaxis or early in treatment, and these findings need to be established for CCP.

There are unique challenges around the collection of CP during a pandemic. These include biological, such as ensuring that donors are clinically and virally free of SARS-CoV-2 and with a sufficient

antibody titre to be therapeutically effective; logistical, such as travel/movement bans; legal, such as donor consent and eligibility, and regulatory requirements for administration of CP in a clinical trial; and scientific, such as limited commercial availability of validated assays for antibody titre testing. National blood services are uniquely positioned to address and manage these challenges, as they are likely to already have appropriate infrastructure and networks to support the rapid collection, testing and storage of blood products such as CP. While studies have shown that CP is safe, the theoretical risks of receiving any blood products need to be considered, including transfusion-transmissible infections and transfusion-related acute lung injury (TRALI), specifically in the setting of a respiratory virus. These risks need to be mitigated by ensuring that CCP donors comply with all standard eligibility and testing criteria established for regular blood donations; excluding parous female donors to reduce the incidence of TRALI; and using pathogen reduction to target transfusion-transmissible infections. Furthermore, there is a theoretical risk that other non-anti-SARS-CoV-2-neutralising antibodies may cause antibody-dependent enhancement of infection. Internationally, the willingness of recovered patients to donate CCP has ensured a sustainable CCP supply.

With no proven effective therapy against COVID-19 available in SA, and in the context of limited resources to provide care to patients with critical illness, it is a research priority to evaluate potential therapeutic interventions in an SA population. An effective vaccine is required for sustained population immunity, but development, manufacture and scale-up are likely to be several months away. It is therefore appealing to consider CCP, which may offer immediate passive immunity, and production of which could be rapidly scaled to be widely available throughout the country in a matter of weeks. However, we would caution that given the current paucity of data and potential risks and complexities, before the use of CCP can be recommended, randomised controlled trials are needed to establish therapeutic efficacy and safe use for COVID-19 disease.

**Conflicts of interest.** VJL is non-executive director of the Board of the Western Cape Blood Service.

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