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Use of convalescent plasma in the treatment of COVID-19

We read with interest the Review "Therapeutic advances in COVID-19" by Murakami et al.[1] and congratulate the authors on their efforts to generate a comprehensive review on this topic. However, the paper is marked by inconsistency in its discussion of convalescent plasma, and we have serious concerns about the authors' dismissal of COVID-19 convalescent plasma (CCP) as an effective treatment for COVID-19, especially in patients with kidney disease who may be immunocompromised.

We provide four reasons that the dismissal of CCP is unwarranted. However, this therapy must be used properly, which is to say, early in the disease course and in the appropriate dose. Many cited randomized controlled trials (RCTs) failed to adhere to these two treatment principles.

First, two well-designed RCTs[2,3] in outpatients clearly demonstrated reduction in clinical deterioration. Murakami et al.[1] cited two negative outpatient trials, but one trial[4] added to their CCP methylene blue, a known antagonist of antibody function, whereas the other[5], which enrolled patients being treated in the emergency room who were not expected to be hospitalized, included admissions on the day of CCP initiation as outcomes. When these admissions, which could not possibly have been affected by CCP treatment given the short time frame, are excluded, CCP significantly reduced hospitalizations[5]. A subsequent preprint patient-level meta-analysis has extended these findings and shown a remarkable reduction in hospitalizations when high-titre CCP was administered early to outpatients[6].

Second, the major negative inpatient treatment trials tested late use of CCP in severe disease, but, nonetheless, all showed positive trends in early-use subgroups with less severe disease, in the immunocompromised, and/or in patients who received the highest titter CCP[7].

Third, in discussing immunocompromised patients, the authors acknowledge that "several observational studies suggested some benefit". In fact, a robust literature of case reports, case series, matched controlled studies and RCTs has emerged showing that CCP is effective in immunocompromised patients with COVID-19. The immunocompromised use case is especially important; our systematic review shows that CCP represents replacement therapy in patients unable to generate endogenous antibody responses to COVID-19 infection[8]. The serial escape from monoclonal antibodies by evolving COVID-19 variants leaves these patients especially vulnerable, and many develop chronic, smouldering infections resistant to other therapies but responsive, as these studies show, to CCP.

Fourth, while the authors point out that older CCP is unlikely to benefit patients infected with newer strains, they fail to note that high-titre CCP collected from contemporaneous patients neutralizes key variants of concern, especially when derived from individuals who have both been vaccinated and recovered from infection, according to our preprint study[9].

Today, CCP has been endorsed for use in immunosuppressed patients by the AABB, IDSA and ECIL and is available worldwide at relatively low cost. The totality of the data indicate that, when used early or in immunocompromised patients, CCP is a highly effective therapy for COVID-19 (ref. [10]).

There is a reply to this letter by Murakami, N. et al. *Nat. Rev. Nephrol.* https://doi.org/10.1038/s41581-023-00691-3 (2023).

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Competing interests

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