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Letter to the Editor

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Too Early to Abandon Convalescent Plasma for Supportive Treatment of COVID-19

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Dear Editor,

A recent report in this journal [1] presents a systematic review and meta-analysis of efficacy and safety of blood derivative therapy for patients with COVID-19, including convalescent plasma (CP) containing antibodies against SARS-CoV-2. The authors conclude that the benefit of CP in the treatment of COVID-19 is limited, while the certainty of the evidence was moderate for all outcomes. The efficacy of CP in COVID-19 was also explored by other systematic reviews [2–4]. While one of them [2] came to the conclusion: "Random effects analyses of randomized clinical trials and matched control data demonstrated that patients with COVID-19 transfused with convalescent plasma exhibited a lower mortality rate compared with patients receiving standard treatments," the other two reviews [3, 4] found no benefit. Should we therefore forget about CP for treating COVID?

The number of published research articles on COVID-19 treatment is huge; a Google Scholar search with the items "COVID convalescent plasma" yields over 40,000 results. In order to keep abreast of such an extensive medical literature, systematic reviews and meta-analyses can be helpful, and it is interesting to have a comprehensive overview of all studies on the use of CP in COVID-19. However, the validity of a meta-analysis depends to a great extent on formulating a focused and meaningful clinical question [5] and including studies which are designed to test a reasonable hypothesis. Normally, in planning clinical trials to support the licensing of medicines, you would aim to define as exactly as possible the investigational drug (composition, dose, and schedule of application) and target disease. In the case of COVID-19, studies have in common the pathogen and CP as investigational treatment, but further details (e.g., duration, stage, and severity of disease and antibody content and dose of CP) are quite heterogeneous [6].

It is understood that the design of clinical CP trials is challenging, both concerning the definition of inclusion and exclusion criteria and the particulars of CP collection, standardization, and dosage. Nevertheless, the so far available evidence suggests that the hypothesis should be sharpened so as to treat COVID-19 patients at risk for

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developing severe disease early enough with a sufficiently high dose of specific antibodies [7]. CP is obtained from individuals who recovered from COVID-19, and it is of course demanding to organize collection and testing of CP with sufficiently high antibody content. However, the importance of the dose is underlined by the recently published follow-up of the CAPSID trial [8], showing in a predefined subgroup analysis a significantly better outcome (long-term survival, time to discharge from ICU, and time to hospital discharge) among those who received a higher amount of neutralizing antibodies compared with the control group. A further challenge is to identify patients early enough, preferably before hospitalization. Nevertheless, it has been demonstrated that such an approach is feasible [9], and it would have been desirable that further trials with a really comparable design would have been conducted in order to strengthen or rebut their conclusion: "Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of COVID-19." The lack of such an independent reproduction can probably not be compensated by compiling all available, heterogenous trials, even with the best methodology of a systematic review and meta-analysis.

The COVID-19 pandemic appears to be fading into an epidemic respiratory infection, owing to immunity of populations by overcoming infection or effective vaccines. However, this should not mean that we may neglect the search for effective prevention and treatments, given the still high death toll of COVID-19. In addition to vaccines, also passive immunization should remain a candidate to be explored. In the above-mentioned systematic review [1], the use of intravenous immunoglobulin was also addressed, which should contain increasing amounts of SARS-CoV-2 antibodies due to infection or vaccination of donors; also, developing specific iv or sc immunoglobulins could be an option. An attractive approach is monoclonal antibodies, which were in fact found effective in the early phase of the pandemic [10]. However, the development of monoclonal antibodies requires advanced technology and time; they are expensive, and unwanted cross-reactivity cannot be excluded. In the meantime, an immune evasion due to new variants of SARS-CoV-2 undermined the efficacy of monoclonal antibodies, which are no longer recommended by the current NIH guidelines [11]. This is a further argument for continuing exploration of CP, which can provide a spectrum of polyclonal antibodies in close timely and regional connection to the particular prevalent virus variant.

Thus, it seems presently premature to remove CP from the list of therapeutic options for COVID-19. On the contrary, it appears to be worthwhile to give CP a further "fair" chance to be evaluated in clinical trials as proactive early treatment with the aim to avoid a severe course and reduce mortality of COVID-19. Moreover, it would be extremely valuable to obtain a solid scientific foundation for the principle of target-specific and temporarily adapted passive immunization, which could be a fast and flexible instrument also in future outbreaks of novel pathogens.

Conflict of Interest Statement

R.S. serves as member of the Data Safety Monitoring Board of the CAPSID and COVIC-19 trials. L.G., U.V., A.H., and W.S. have no conflicts of interest to declare.

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Author Contributions

R.S. wrote the manuscript. L.K., U.V., A.H., and W.S. contributed to the concept and conclusions.

References

1 Fei Z, Chen Z, Du X, Cao H, Li C. Efficacy and safety of blood derivative therapy for patients with COVID-19: a systematic review and meta-analysis. Transfus Med Hemother. 2022;382(6):1–13.

2 Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, et al. The effect of convalescent plasma therapy on mortality among patients with COVID-19: systematic review and meta-analysis. Mayo Clin Proc. 2021;96(5):1262–75.

3 Bansal V, Mahapure KS, Mehra I, Bhurwal A, Tekin A, Singh R, et al. Mortality benefit of convalescent plasma in COVID-19: a systematic review and meta-analysis. Front Med. 2021;8:624924.

4 Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimi F, Hepprich M, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19. A systematic review and meta-analysis. JAMA. 2021;325(12):1185–95.
5 Crowther MA, Cook DJ. Trials and tribulations of systematic reviews and meta-analyses. Hematol Am Soc Hematol Educ Program. 2007;2007(1):493–7.
6 Müller-Olling M, Vahlensieck U, Hilger A. Heterogeneity in COVID-19 convalescent plasma clinical trials. Clin Pharmacol Ther. 2022 May;111(5):995–1000.
7 Seitz R, Gürtler L, Schramm W. COVID-19 convalescent plasma: No definite answer yet. J Blood Lymph. 2021;11:265–7.
8 Körper S, Grüner B, Zickler D, Wiesmann T, Wuchter P, Blasczyk R, et al. One-year follow-up of the CAPSID randomized trial for high-dose convalescent plasma in severe COVID-19 patients. J Clin Invest. 2022; 132(24):e163657.
9 Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early high-titer plasma therapy to prevent severe covid-19 in older adults. N Engl J Med. 2021;384(7):610–8.
10 Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with covid-19. N Engl J Med. 2021;385(23):e81.
11 Coronavirus NIH. Disease 2019 (COVID-19) treatment guidelines. Downloaded from https://www.covid19treatmentguidelines.nih.gov/.