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Convalescent plasma for covid-19

Authorisation in the US was premature, and a missed opportunity

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Plasma from people recovering from infection, particularly after severe illness, may contain high levels of polyclonal, pathogen specific antibodies. These antibodies may confer passive immunity to recipients, and in viral diseases are thought to act mainly by neutralising viral particles.¹ Convalescent plasma, or purified antibodies from the plasma (hyperimmune globulin), was often used in clinical practice before the advent of vaccines, including during the influenza pandemic of 1918.² Hyperimmune globulin is still used for post-exposure prophylaxis against various viral infections, including hepatitis B, varicella zoster, and rabies.

The use of convalescent plasma to treat patients with covid-19 has understandably attracted a lot of attention, but definitive evidence of efficacy has been elusive. Nevertheless, on 23 August the US Food and Drugs Administration authorised its emergency use for hospital patients with covid-19. At the time, only two small underpowered trials had been published.^{3,4}

Until this authorisation the large scale clinical administration of convalescent plasma in the US was regulated under the FDA's expanded access treatment protocol, which required individual patient authorisation and collection of data on clinical outcomes and side effects. Over five months, from 1 April 2020, the protocol served over 2700 hospitals and enrolled over 100 000 patients.⁵ The initial purpose of the data collection was to establish the safety of convalescent plasma.⁶ However, the data were also analysed for signals of efficacy, despite a lack of control data from patients treated without convalescent plasma. After reviewing these analyses and other experimental and historical data, the FDA judged that convalescent plasma "may be effective" and was therefore eligible for wider use under an emergency use authorisation.⁷ All adults being treated for covid-19 in US hospitals can now be given convalescent plasma.

Although the FDA still states that "Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of CCP [convalescent plasma] efficacy and to determine the optimal product attributes and appropriate patient populations for its use," doctors and hospitals are no longer obliged to report data on clinical outcomes. The only requirement is to report deaths related to transfusion.⁸ Experts argue that the emergency use authorisation will make it more difficult to recruit participants for randomised trials of convalescent plasma in the US.

What other evidence underpinned the FDA's controversial decision? The most recent version of the Cochrane living systematic review on convalescent plasma⁹ was available, along with more

recent randomised and non-randomised studies.^{4,10-15} However, the only two randomised trials (189 participants in total)^{3,4} could not be combined in meta-analyses because they used different times for assessing mortality and different rating scales for clinical outcomes. Meta-analysis of individual patient data would overcome these problems and should be done. Even if these small trials could be combined, the analyses would not be powerful enough to detect a significant difference in all-cause mortality, arguably the most important outcome, and a conclusive meta-analysis may require inclusion of data from the many randomised trials currently in progress.

For safety data, the FDA relied mainly on the expanded access programme,⁶ which collected data on serious adverse events among the 20 000 patients treated with convalescent plasma. The incidence of adverse events related to transfusion (transfusion associated circulatory overload, transfusion related acute lung injury, and severe allergic reactions) in the first four hours after transfusion was low (<1%), and the immediate risks associated with convalescent plasma transfusions are widely agreed to be no greater than those associated with transfusions of standard plasma. Crucially, there has been no evidence so far of antibody mediated enhancement of disease in covid-19 patients given convalescent plasma despite suggestions that this might be a possibility in the presence of reactive but non-neutralising antibodies against SARS-CoV-2.^{16, 17}

The US National Institutes of Health and the FDA are clear that efficacy of convalescent plasma for covid-19 is not yet established and that every effort should be made to complete further randomised trials.⁷ At least 73 trials are already underway worldwide. No country, including the US, has licensed convalescent plasma as a treatment for covid-19, although other countries have granted approval for use on an individual patient basis.

The lack of randomised trial evidence from the US reflects a missed opportunity. If large simple trials had started in the US at the same time as the extended access programme, we would already know whether convalescent plasma is effective and safe. The UK has shown that large simple trials, such as the RECOVERY trial, are feasible and can provide answers to important therapeutic questions during a pandemic.¹⁸ The RECOVERY and REMAP-CAP trials are both evaluating convalescent plasma in patients with covid-19 being treated at 190 hospitals in the UK. Results are expected by the end of 2020, although completion ultimately depends on rates of admission for covid-19 in participating hospitals.

What is certain is that high quality evidence from randomised controlled trials is needed to drive the development of large-scale plasma collection internationally, to inform reliable guidelines for clinical use, and to provide the maximum benefit to patients.

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