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Convalescent plasma contains antibodies and immune proteins that could help treat disease.

US WIDENS ACCESS TO COVID-19 PLASMA — DESPITE LACK OF DATA

Emergency authorization could threaten trials to learn whether the blood product works as a therapy.

By Heidi Ledford

US regulators have authorized the use of blood plasma from COVID-19 survivors as a treatment for the disease, widening access to the therapy. But the move, announced by President Donald Trump in a press conference on 23 August, could undercut the clinical trials trying to determine whether it works, researchers warn.

Although some US hospitals already offered the treatment in special cases, an emergency-use authorization from the Food and Drug Administration (FDA) makes it easier to obtain and administer convalescent plasma — the yellow liquid that remains after cells are removed from blood.

So far, the experimental therapy has been tested only in small trials without the statistical power to provide firm conclusions. In a statement, the FDA says the authorization "is not intended to replace randomized clinical trials". It adds that facilitating "ongoing randomized clinical trials is critically important for the definitive demonstration of safety and efficacy of COVID-19 convalescent plasma". Experts say, however, that because of the FDA's action, people with COVID-19 might choose to access the treatment directly, rather than sign up for a clinical trial and risk being assigned to a control group given a placebo.

"It's a potential therapy that could work," says former FDA commissioner Robert Califf, who now heads clinical policy and strategy at Verily and Google Health in South San Francisco, California. "But we ought to be really emphasizing in public-service announcements that participation in randomized trials is a first priority."

Missing evidence

For more than a century, doctors have used the convalescent plasma of donors recovering from infections to treat others with the same disease, including Ebola. The idea is that plasma contains antibodies and other immune proteins. And some of these antibodies might have helped the donor to recover from their infection — so giving it to infected people could kick-start their recovery. It was logical to test the treatment against COVID-19 when the outbreak began, but researchers have struggled to nail down its effectiveness in the middle of the pandemic, says Michael Joyner, an anaesthesiologist at Mayo Clinic in Rochester, Minnesota.

Collecting rigorous clinical-trial data has been difficult because doctors have been administering convalescent plasma to severely ill people on a 'compassionate use' basis. In the United States, a special programme funded by the Biomedical Advanced Research and Development Authority (BARDA) has provided blood plasma on this basis to more than 70,000 people — without running any control groups. The programme's investigators — including Joyner — have been gathering data and have published results from 5,000 people with severe COVID-19, suggesting that the therapy is broadly safe (M. J. Joyner *et al. J. Clin. Invest.* http://doi.org/d65h; 2020).

In the absence of a control group, Joyner and his colleagues have taken advantage of the fact that the concentration of SARS-CoV-2 antibodies in donated plasma varies. The team looked at more than 35,000 plasma recipients, and compared results from those who received plasma that had relatively low levels of antibodies with findings from people who got plasma with higher levels. The study, published on the medRxiv preprint server before peer review, found that participants who received transfusions soon after their diagnosis and got high levels of antibodies showed more improvement and were less likely to die in the study period than were those who received later transfusions with lower antibody levels (M. J. Joyner *et al*. Preprint at medRxiv http://doi.org/d65j; 2020).

But the lack of randomization makes it difficult to draw a firm conclusion from the study, cautions Anthony Gordon, an anaesthetist at Imperial College London. For example, patients who received the treatment soon after diagnosis might have been treated at medical centres that provided better health care, he says, raising their chance of a better outcome. "We're just seeing an association," he says. "We're not seeing cause and effect."

There are still data to come. In the United Kingdom, epidemiologist Martin Landray and infectious-disease researcher Peter Horby, both at the University of Oxford, are leading the large RECOVERY trial, which is testing several therapies, including convalescent plasma, in people hospitalized with COVID-19. And Gordon and his colleagues are testing convalescent plasma in people in intensive care, in an international trial called REMAP-CAP. But the first surge of the pandemic in the United Kingdom has largely passed, so Landray says that he does not expect to have results until later in the year, when some epidemiological models predict COVID-19 cases will rise again.

"There is good science behind convalescent plasma and a good reason for thinking that it may turn out to be an effective treatment," Landray says. "But the bottom line is that we don't have enough data to know."