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FOR people who have survived covid-19, there is an opportunity to add another chapter to their recovery story: they could help save other people's lives by donating blood.

The plasma of people who have recovered from the disease contains precious antibodies that helped them fight off the virus, and could help others do the same, or even make them temporarily immune. Such antibodies are an increasing focus of research efforts to treat and prevent covid-19. According to senior US health official Anthony Fauci, antibody therapies could be a “bridge to a vaccine” – a stopgap to carry us safely to the promised land.

The use of antibody-laden blood plasma was developed more than 100 years ago to treat diphtheria. It fell out of favour with the introduction of antibiotics, but was revived in 2002 during the SARS epidemic, and has since been used against Ebola and H1N1 flu. Another reason for plasma injection is to provide “passive” immunity, effectively a short-term vaccine for diseases such as hepatitis B.

Ready-made therapy
The research for using several types of plasma to treat covid-19 is still in its early stages. The most basic antibody therapy is convalescent plasma. The idea is simple: transfuse plasma from a recovered patient into a sick person's bloodstream to give them an instant immune response. “It's appealing because it's a ready-made potential therapeutic,” says Jeffrey Sturek at the University of Virginia, who is running a convalescent plasma trial. “You can also borrow immunity from other people.”

Plasma is the liquid part of blood, and donating it is similar to blood donation. Blood is siphoned from a vein in the arm, but then separated using a process called plasmapheresis. The plasma is retained but the red and white blood cells are infused back into the donor. Plasma infusions are similar to blood transfusions. The plasma is screened for pathogens, tissue-matched, then infused into the bloodstream.

There are no approved convalescent plasma therapies for covid-19 yet, but some small-scale pilot studies have reported benefits for very ill people. In August, the US Food and Drug Administration (FDA) granted the therapy an emergency use authorisation (EUA), which means it can be given to patients despite not having jumped through all the regulatory hoops. More than 50 clinical trials are under way, some looking at it as a vaccine.

As yet “there is only limited data”, says Diana Gabriela Iacob at the National Institute of Infectious Diseases in Bucharest, Romania, who has published a review of potential covid-19 treatments. Some side effects have been reported, including risk of lung injury. However, Sturek says it is no more risky than a routine plasma transfusion.

“We're hopeful,” he says. “We do lack the level of evidence from a randomised controlled trial, but what's the harm? It may be helpful and it's probably safe.”
people in India, announced that there was no clinical benefit. However, that was just one small treatment trial and the plasma levels of antibody used were low. “There may be ways to refine it as a treatment and deliver solid, demonstrable benefits,” said Simon Clarke at the University of Reading, UK, in a statement.

There is also the issue of antibody-dependent enhancement, where an antibody backfires and makes the disease worse. However, this is a “somewhat theoretical risk”, says Sturek. It is very rare in other infectious diseases and hasn’t yet been seen in covid-19. The therapy also depends on a steady supply of convalescent donors, but they aren’t hard to persuade, he says. “There is a sense of gratitude and wanting to give back.”

**Turbo-charged plasma**

Another approach called hyperimmune globulin (H-Ig) is also showing promise. This is essentially turbo-charged convalescent plasma that has been pooled, purified and concentrated. H-Ig is already used against numerous conditions including flu and other respiratory viruses.

There are four covid-19 H-Igs in development, two from a consortium of companies called the Plasma Alliance.

This approach is attractive because “it’s cleaner and more consistent; you have a better idea what you’re giving the patient”, says Sturek. This is because standard convalescent plasma contains a variable amount of the desired antibodies, and might also contain toxins or other nasties.

But whereas convalescent plasma can be dispensed immediately, H-Ig takes time to prepare and scale up. You also need several donors to make one dose, but in return “you get a more consistent antibody potency and more antibody in a smaller volume”, says Lutz Bonacker at CSL Behring in Hattersheim am Main, Germany, one of the companies in the alliance. All four H-Igs are being tested in a single trial as therapy for hospitalised patients in 18 countries. The trial is in phase III, assessing effectiveness, and could finish before the end of the year.

The next level up is monoclonal antibodies. The principle is the same, but the production method is different. The antibodies aren’t extracted directly from plasma, they are pumped out by genetically modified cells.

The first step is to screen convalescent plasma to find the most potent antibodies, and then engineer cells to produce them in large quantities. Monoclonal antibodies are already used for hundreds of diseases, including cancers, autoimmune diseases and some infectious diseases.

The leading player for covid-19 is biotech company Regeneron in New York, which hit the headlines after its experimental therapy REGN-COV2 was administered to US president Donald Trump. It is a cocktail of two monoclonal antibodies selected for their ability to block the virus from entering cells, and is in clinical trials both as a therapy and a prophylactic.

Regeneron has said that people with confirmed cases who are given the antibody cocktail have a lower viral load, get better faster and need less medical attention. It hasn’t revealed results from the prevention side of the trial.

Two days after Trump left hospital in October having extolled Regeneron’s virtues, the firm and its main rival, Eli Lilly, asked the FDA for an EUA for monoclonal antibody treatments. The FDA hasn’t yet responded.

Results of monoclonal antibody trials released so far, which are mostly in animals, look good, and it is “plausible” that it will work in humans, says Robin Ferner at the University of Birmingham, UK, who assessed Regeneron’s drug for the UK’s Centre for Evidence-Based Medicine. He says a similar approach was tested on Ebola in 2018 and worked “somewhat”.

However, monoclonal antibodies aren’t a sure-fire success. Despite the production method not relying on donors, making large quantities is a challenge. Regeneron says it has enough of one of its monoclonal antibodies to treat just 50,000 people. “Costs are likely to be eye-watering,” says Ferner.

There are also likely to be other roadblocks. Days after asking for an EUA, Eli Lilly halted recruitment for one of its clinical trials on the advice of a safety monitoring board. But the company has three other ongoing trials.

On 28 October, it published positive interim results from one of these, in people with mild or moderate covid-19 who hadn’t been admitted to hospital. Those who had the treatment were less likely to end up in hospital (NEJM, doi.org/fgtm). The results have been peer-reviewed.

Aside from the Regeneron and Eli Lilly ones, at least two other monoclonal antibody trials are under way.

If antibody therapies succeed, the analogy of them being a bridge to a vaccine is a good one, says Sturek. But even when a vaccine is available, that bridge will still be needed. “Not everyone will respond well to a vaccine,” says Sturek. For those people who don’t get protection from vaccines, antibodies could be their only route to immunity.