The role of antibodies in Covid-19 treatment

In mid-September 2020, researchers at the University of Pittsburgh School of Medicine in the US announced that they had identified an antibody component that exhibits high affinity for the spike protein of the SARS-CoV-2 virus but which is just one-tenth the size of a normal antibody. The component also displayed high prophylactic and therapeutic efficacy in rodent models of SARS-CoV-2 infection.

The component is the variable heavy chain (V_H) domain of a human immunoglobulin and was selected from a large library of human antibody V_H domains. The researchers have fused the VH domain to part of the immunoglobulin tail region to create a drug candidate, Ab8, with the immune functions of a full-sized antibody but without the bulk. The small size of the molecule is claimed to increase its potential to diffuse into tissues and could make it easier to administer to patients, for example via inhalation. Abound Bio, a company spun out of the University of Pittsburgh Medical Center that specialises in antibody library applications, has licensed Ab8 for worldwide development.

The Pittsburgh announcement was just one example of the continuing interest in the use of antibody-based therapies to treat Covid-19 disease. This interest is rooted in the use of convalescent plasma to treat the disease, and has led a number of companies to investigate the potential of monoclonal antibodies against SARS-CoV-2 proteins to treat Covid-19. In addition, some companies have begun to assess monoclonal antibodies originally developed for other indications for their usefulness in treating Covid-19 symptoms related to overreaction of the body's immune system.

Therapies based on anti-SARS-CoV-2 antibodies have many potential uses, including prophylactically to boost to the immune system to protect healthcare workers, or the elderly, who may not respond so well to a vaccine, as well as therapeutically to combat the disease in individuals who have already been infected with the virus. An executive at Eli Lilly and Co has suggested that antibody treatments could serve as a bridge until vaccines are available. The potential of antibody therapeutics was dramatically illustrated on 2 October when it was reported that US President Donald Trump was given an experimental antibody cocktail developed by Regeneron Pharmaceuticals Inc to treat his infection with SARS-CoV-2. The product, REGN-COV2, was administered on a compassionate use basis.

Proponents of therapeutic antibodies also point out that they may be acceptable to individuals reluctant to accept a vaccine, and that in any case vaccines are rarely 100% effective. On the other hand, it may not be possible to manufacture monoclonal antibodies on as large a scale as vaccines, and antibodies are likely to be more expensive than vaccines. These factors raise questions about whether antibodies would be accessible to everyone who needed them.

Convalescent plasma

The role envisioned for antibodies in the prevention and treatment of Covid-19 has its origins in convalescent plasma therapy, the practice of administering plasma from patients who have recovered from an infectious disease to patients with active infections. The rationale is that antibodies against the pathogen in the plasma provide the recipient with passive immunity. Convalescent plasma therapy has a long history and was widely used to treat bacterial infections before the advent of antibiotics. The technique is still often used to treat viral infections for which chemotherapeutic agents do not exist, such as new epidemic diseases. In the Ebola outbreak of 2014, for example, convalescent plasma treatment was credited with improving survival compared with standard treatment.

According to CSL Behring, which describes itself as the world's largest collector of human plasma, there are two ways that plasma treatments might help fight Covid-19. In the first, plasma collected from patients who have recovered from Covid-19 is infused directly into patients experiencing serious Covid-19 complications, an approach which is the subject of multiple clinical trials in the US and elsewhere. One potential snag with this approach is that the amount of antibodies in the plasma may vary, making standardisation of therapy difficult. In the second approach, pooled plasma from multiple donors is processed to create a hyperimmune globulin that contains a consistent amount of antibodies, making it much easier to standardise treatment.

CSL Behring is one of six companies – the others are Biotest AG, Bio Products Laboratory Ltd, LFB SA, Octapharma AG, and Takeda Pharmaceutical Company Ltd – that earlier this year came together to form the CoVIg-19 Plasma Alliance. The aim of the Alliance is to accelerate the development and supply of CoVIg-19, a Covid-19 hyperimmune globulin. The alliance is supported by The Bill & Melinda Gates Foundation and by Microsoft Corp, which is hosting the Plasma Alliance plasma donor recruitment website and providing other patient support. Since its creation, the Alliance has been joined by several other industry members.

In general, Big Pharma companies seem to have eschewed the convalescent plasma approach to Covid-19, although there is a sizeable number of trials being conducted by hospitals or academic groups. Part of this reluctance may be put down to the fact that, to date, evidence of the effectiveness of convalescent plasma is limited. A review of the use of convalescent plasma and hyperimmune globulin, published by the Cochrane Library earlier this year, expressed uncertainty as to whether convalescent plasma is beneficial for people admitted to hospital with Covid-19. Specifically, the authors said they doubted whether convalescent plasma has any effect on all-cause mortality at hospital discharge, whether it prolongs time to death, or whether it has any effect on the improvement of clinical symptoms at seven days. Furthermore, among the 20 studies reviewed by the Cochrane Library, there was limited information regarding adverse events.

Nevertheless, in August 2020 the US Food and Drug Administration issued an emergency use authorisation (EUA) for investigational convalescent plasma for the

treatment of Covid-19 in hospitalised patients. Based on a review of evidence using convalescent plasma in other infections and from small clinical trials of convalescent plasma conducted during the current outbreak, as well as other sources, the FDA concluded "… it is reasonable to believe that the known and potential benefits of Covid-19 convalescent plasma outweigh the known and potential risks of the drug for the treatment of patients hospitalised with Covid-19".

Separately, the FDA has issued guidance for the use of Covid-19 convalescent plasma in clinical trials.

The European Commission is also supporting research on convalescent plasma to treat Covid-19. On 11 September, it announced a new EU-funded research project, SUPPORT-E, to determine whether Covid-19 convalescent plasma transfusion is an effective and safe treatment. The €4 million project is being led by the European Blood Alliance and involves 12 major research establishments in six EU countries, Switzerland and the UK.

Monoclonal antibodies

The debate about the effectiveness of convalescent plasma therapy has not deterred some major pharma companies, including AstraZeneca Plc, Eli Lilly and Co, GlaxoSmithKline Plc and Regeneron, from exploring the use of specific anti-SARS-CoV-2 antibodies in the treatment of Covid-19. One of the most advanced is Regeneron, whose REGN-COV2 product, mentioned earlier, is a combination of two anti-spike monoclonal antibodies, REGN10933 and REGN10987. The company says it believes that using a combination of antibodies is less likely to lead to the emergence of resistant strains of the virus.

REGN-COV2 is currently being studied in several late-stage clinical trials, including: an open-label, Phase 3 trial of hospitalised Covid-19 patients in the UK, part of the RECOVERY (Randomised Evaluation of COVid-19 thERapY) study; a Phase 3 trial in the US for the prevention of Covid-19 in uninfected people who are at high-risk of exposure to a Covid-19 patient (such as the patient's housemate); and two US Phase 2/3 trials for the treatment of hospitalised and ambulatory Covid-19 patients respectively. The Phase 3 prevention trial is being jointly conducted with the National Institute of Allergy and Infectious Diseases (NIAID).

At the end of September, Regeneron released the first data from a descriptive analysis of a seamless Phase 1/2/3 trial of REGN-COV2. Among ambulatory patients with Covid-19 REGN-COV2 reduced viral load and the time to alleviate symptoms. The biggest responses were seen in patients who had not mounted their own effective immune responses to the virus prior to treatment.

Another front-runner in the use of monoclonal antibodies to treat Covid-19 is Lilly. In March 2020 it announced a tie-up with the Canadian therapeutic antibody company AbCellera Biologics Inc to co-develop antibody products for the prevention and treatment of Covid-19. In mid-September the two companies announced that interim data from a Phase 2 trial of LY-CoV555, the first antibody to emerge from the collaboration, showed that the rate of hospitalisations and visits to the emergency room in patients treated with the antibody was 1.7% (five out of 302 patients) for LY-CoV555 compared with 6% (nine out of 150) for placebo. LY-CoV555 was well-tolerated, with no drug-related serious adverse events reported.

LY-CoV555 is a neutralising IgG1 monoclonal antibody directed against the spike protein of SARS-CoV-2, and is based on an antibody identified in the blood of a recovered Covid-19 patient using AbCellera's pandemic response platform. The technology was developed as part of the US Defense Advanced Research Projects Agency (DARPA) Pandemic Prevention Platform programme. LY-CoV555 is also being studied as part of ACTIV-3, one of four trials in the National Institutes of Health's Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) programme.

Meanwhile GSK is collaborating with the clinical-stage immunology company Vir Biotechnology Inc to research and develop therapeutic candidates for preventing or treating infections with coronaviruses, including SARS-CoV-2. The collaboration is designed to exploit Vir's proprietary monoclonal antibody platform technology and GSK's expertise in functional genomics. As part of the collaboration, announced earlier this year, GSK made an equity investment in Vir of $250 million.

At the beginning of October, the two companies announced that they had got the go-ahead to expand the COMET-ICE (Covid-19 Monoclonal antibody Efficacy Trial – Intent to Care Early) trial, which aims to assess the safety and efficacy of VIR-7831, into Phase 3. Also known as GSK4182136, VIR-7831 is a fully human anti-SARS-CoV-2 monoclonal antibody being developed for the early treatment of Covid-19 in patients who are at high risk of hospitalisation. The primary goal of the trial is to assess whether a single dose of VIR-7831 can prevent hospitalisation due to Covid-19 in high-risk individuals who have early symptomatic infection. According to the companies, initial results of the trial may be available before the end of 2020, with complete results anticipated in the first quarter of 2021. Future studies are planned to assess the antibody's ability to prevent infection in high-risk individuals and reduce disease severity in patients who are already hospitalised.

Also as part of the collaboration, the two companies are investigating a second monoclonal antibody, VIR-7832, which has been engineered to enhance its bioavailability in the lung, have an extended half-life, and potentially function as a therapeutic and/or prophylactic T cell vaccine.

Somewhat further back along the development pipeline is AstraZeneca's AZD7442, which recently entered Phase 1 trials. Like the Regeneron product, AZD7442 is a combination of two monoclonal antibodies, in this case derived from convalescent patients recovering from SARS-CoV-2 infection. The antibodies were discovered at Vanderbilt University Medical Center and licensed to AstraZeneca in June 2020. The company then modified the antibodies to extend their half-lives and to reduce Fc receptor binding. Data readout from the Phase 1 study is expected later this year.

Other companies active in the antibody space include Sorrento Therapeutics Inc, which has begun Phase 1 trials with COVI-GUARD, a neutralising antibody which binds to the S1 subunit of SARS-CoV-2 spike protein. Also in preclinical development at Sorrento are COVI-SHIELD, a

neutralising antibody cocktail that binds to distinct epitopes on SARS-CoV-2 spike protein, and COVIDTRAP, an ACE2-Fc decoy protein that binds strongly to the spike protein of the SARS-CoV-2 virus. The Chinese company Sinocelltech is conducting Phase 1 trials of SCTA01, an anti-SARS-CoV-2 monoclonal antibody, while Singapore-based Tychan Pte. Ltd has begun Phase 1 trials of its SARS-CoV-2 monoclonal antibody, TY-027. Lastly, Shanghai Junshi Biosciences Co Ltd is carrying out an early clinical trial of its anti-SARS-CoV-2 neutralising monoclonal antibody, JS016. Earlier this year, the company announced a research collaboration and licence agreement with Lilly in respect of JS016.

Immune modulators

While the above companies are investigating the use of anti-SARS-CoV-2 antibodies in the treatment of Covid-19, other groups have turned their attention to the cytokine release syndrome that is believed to underlie many of the more serious complications of Covid-19. The main antibodies being investigated are summarised here:

- Ilaris (**canakinumab**) is a human monoclonal antibody targeted at interleukin-1β developed by Novartis for the treatment of systemic juvenile idiopathic arthritis and active Still's disease. It is undergoing an international randomised, controlled Phase 3 trial to assess its efficacy and safety in patients with Covid-19-induced pneumonia and cytokine release syndrome.
- Janssen's (J&J's) Remicade (**infliximab**) is a recombinant chimeric human-mouse IgG monoclonal antibody used to treat a number of autoimmune diseases. It is under investigation at Tufts Medical Center in Boston, Massachusetts, US, for its ability to prevent further clinical deterioration and reduce the need for advanced cardiorespiratory support and early mortality in severe Covid-19.
- **Otilimab** is an investigational anti-granulocyte-macrophage colony stimulating factor (GM-CSF) human antibody developed by MorphoSys AG and under investigation by GSK for the treatment of severe pulmonary Covid-19 related disease.
- Ultomiris (**ravulizumab**) is a humanised monoclonal antibody complement inhibitor developed by Alexion Pharmaceuticals Inc and indicated for the treatment of paroxysmal nocturnal haemoglobinuria. It is the subject of an international Phase 3 study in adult patients with Covid-19 severe pneumonia, acute lung injury, or acute respiratory distress syndrome.
- Kevzara (**sarilumab**) is a human monoclonal antibody against the interleukin-6 receptor developed by Regeneron and Sanofi SA for the treatment of rheumatoid arthritis which was approved in the US in 2017. In July, the companies announced that a US Phase 3 trial of Kevzara in Covid-19 patients requiring mechanical ventilation did not meet its primary and key secondary endpoints when Kevzara was added to best supportive care compared to best supportive care alone.
- Actemra (**tocilizumab**) is a monoclonal antibody against the interleukin-6 receptor originally developed by F Hoffmann-La Roche AG for the treatment of rheumatoid arthritis. It was approved by the FDA in 2017 for the additional indication of cytokine release syndrome associated with CAR T-cell therapy. In a multicentre retrospective observational study published in *The Lancet* in August 2020, use of tocilizumab in patients with severe Covid-19 was associated with an improvement in median overall survival. Patients with elevated C-reactive protein levels were the most likely to benefit from tocilizumab treatment.

Meanwhile, interest in therapeutic antibodies is still growing. For example, in May of this year, two contract research organisations that specialise in antibody discovery services, Iontas Ltd and FairJourney Biologics SA, joined forces to offer antibody discovery and other services. By the end of September, the two companies had identified the sequences of several hundred antibodies that bind SARS-CoV-2 from the sera of Covid-19 patients. After purification and *in vitro* screening, a panel of 15 antibodies was selected based on their potent neutralising ability and biophysical characteristics suited for downstream development and manufacture. The antibodies are now expected to enter further preclinical testing and development.

This article was written by Peter Charlish, PhD, a contributing editor to *MedNous*, and former editor at Informa Plc.

