VIEWPOINT

Monoclonal Antibodies for Prevention and Treatment of COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic has created a worldwide crisis and inspired an urgent search for prevention and treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Attention has focused on the development of vaccines, new antiviral agents, and convalescent plasma infusions. Monoclonal antibodies have received less attention even though neutralizing antibodies are a key component of protective immunity for most viral diseases. Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential for both therapeutic and prophylactic applications, and can help to guide vaccine design and development.[1]

Since the identification of SARS-CoV-2 as the causative agent of COVID-19, numerous research groups have isolated monoclonal antibodies (most often from the B cells of patients who have recently recovered from SARS-CoV-2, and in some cases from individuals who were infected with the severe acute respiratory syndrome coronavirus [SARS-CoV] in 2003). It is also possible to generate effective monoclonal antibodies by immunization of humanized mice. Modern methods allow the rapid identification of pathogen-specific B cells and recovery of immunoglobulin heavy chain and light chain genes that can be expressed to produce monoclonal antibodies, usually in the form of IgG.

The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Essentially all monoclonal antibodies of interest target this protein. Viral infection is mediated by the interaction between the viral spike and the angiotensin-converting enzyme 2 (ACE 2) receptor found on numerous cell types, but neutralizing monoclonal antibodies block this event. Although current knowledge is increasing about the epitopes present on the SARS-CoV-2 spike protein, prior knowledge of other human coronaviruses has facilitated rapid advances in understanding the atomic level structure of the spike protein.[2] The majority of monoclonal antibodies isolated to date specifically target the receptor-binding domain on the spike protein that allows SARS-CoV-2 to make contact with the ACE 2 receptor.[3,4] However, based on current knowledge of SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), it is likely that neutralizing antibodies can target other regions of the spike protein as well.[5] Neutralizing monoclonal antibodies are often characterized by their potency in vitro in a variety of cell culture assays, which is an important attribute used to help select monoclonal antibodies with potential for clinical use.

The Clinical Utility of Monoclonal Antibodies

SARS-CoV-2 monoclonal antibodies have the potential to be used for both prevention and treatment of infection. Benefits have been demonstrated in animal models for both SARS-CoV and MERS-CoV monoclonal antibodies. Most people recovering from SARS-CoV-2 infection will generate a cellular and humoral immune response against SARS-CoV-2. Given the lack of effective therapies for patients with advanced COVID-19, several groups have collected convalescent plasma and measured SARS-CoV-2 neutralization titers. In the largest study to date, Joyner et al[6] administered 1 to 2 units of convalescent plasma to 5000 patients with severe or life-threatening SARS-CoV-2 infection. The investigators reported an incidence of less than 1% for severe adverse events and a 7-day mortality rate of 14.9%, which is consistent with the natural history of severe infection.[6]

Liu et al[7] reported a benefit from convalescent plasma with a neutralizing titer dilution of greater than 1:320 when provided to hospitalized patients who did not require intubation. Further assessment of the potential clinical benefits of convalescent plasma is anticipated. The limitations of convalescent plasma include the difficulty in collection, variability of binding and neutralizing antibody titers, potential contamination with infectious agents, risk of transfusion reactions, and circulatory overload associated with administration. However, success in convalescent plasma research serves to inspire development and deployment of monoclonal antibodies.

Treatment With Monoclonal Antibodies

Even though more than 75 monoclonal antibodies have been licensed for use by the US Food and Drug Administration, only 3 are used to treat or prevent infectious diseases—respiratory syncytial virus, anthrax, and *Clostridioides difficile*. Two different monoclonal antibody products have been shown to be effective in reducing mortality from Ebola virus disease,[8] especially if used during early onset of infection. One of these was a combination of 3 monoclonal antibodies, while the other was a single monoclonal antibody. The successful treatment of an aggressive fatal virus supports the potential of monoclonal antibodies for the treatment of COVID-19.

Several SARS-CoV-2 monoclonal antibodies are poised to enter clinical trials during the summer of 2020. Therapeutic trials will include treatment of patients with SARS-CoV-2 infection, with varying degrees of illness, to block disease progression. Given the long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), a single infusion should be sufficient. Most patients with SARS-CoV-2 infection (in the absence of advanced age or comorbidities) will recover without treatment, albeit at variable rates, emphasizing the need to study monoclonal antibodies in patients most likely to benefit from early monoclonal antibody therapy. A potential limitation of

monoclonal antibodies for treatment of COVID-19 is the unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs, which serve as a key target of SARS-CoV-2 infection. Another consideration is the effect of viral diversity, so it will be important to monitor for the emergence of resistant viral mutations under selective pressure of monoclonal antibody treatment. Accordingly, monoclonal antibodies have been chosen to target conserved regions of the viral spike and some products will include of a combination of 2 monoclonal antibodies targeting different sites on the spike protein.

Prevention

An effective vaccine is a necessary solution to the COVID-19 pandemic. Although the vaccine development process generally takes years or even decades, aggressive efforts to evaluate several COVID-19 vaccine candidates concomitantly are planned to shorten the development process to 12 to 18 months.[9] Monoclonal antibodies provide an alternative avenue for the prevention of COVID-19. Passive infusion of monoclonal antibodies as preexposure or postexposure prophylaxis might offer immediate protection from infection that could last weeks or months. Newer technologies that modify the Fc region of the antibody to extend the half-life of monoclonal antibodies can provide potentially protective levels for months, depending on the monoclonal antibody concentrations required.

Even if a vaccine is available, the weeks of time required to generate an effective immune response emphasizes the benefits of passive immunity in a variety of circumstances including health care settings, households, and facilities where outbreaks have been common and devastating. Nursing homes and meat-packing plants have experienced large SARS-CoV-2 outbreaks. Monoclonal antibodies administered to nursing home residents during an outbreak might also serve to limit the progression of disease during undetected early infection. In addition, older individuals and those with underlying comorbid conditions might not mount a robust protective response after vaccination, and so monoclonal antibodies may be required to provide protection.

Challenges

There are substantial challenges to demonstrating the benefits of monoclonal antibodies in clinical trials. Because most people with early infection recover, the clinical end points needed to demonstrate a benefit relative to placebo are not easily achieved. Likewise, it may be difficult to demonstrate benefit in patients with more severe disease, in whom inflammation and coagulopathy may be more important than viral replication. For monoclonal antibody prevention trials, the difficulty is finding individuals at sufficient risk (ie, a high enough attack rate) to demonstrate prevention of symptomatic infection. As the COVID-19 pandemic evolves across the US and the world, the clinical research infrastructure will require the flexibility to provide monoclonal antibodies on short order to populations or facilities at high risk of infection. Another potential challenge is the ability to produce enough monoclonal antibody product. Although this will be influenced by the dose required and may differ for prevention and treatment, current commercial manufacturing capacity can likely produce millions of doses annually.

There is also some concern for immune enhancement of COVID-19 because vaccine-associated enhanced disease has been observed in animal models of SARS-CoV and for other animal coronaviruses. Categories of possible disease enhancement include antibody-mediated enhancement of viral entry and replication in target cells (Fc-bearing monocytes or macrophages) and virus-antibody immune complexes and the associated cytokine release. For the former, antibody-mediated enhancement is classically defined as Fcγ-receptor–mediated enhanced disease in the presence of subneutralizing concentrations of antibodies or nonneutralizing antibodies.[10]

Conclusions

Neutralizing antibodies have an important role in the protection or recovery from many viral infections. Several monoclonal antibody products will enter clinical trials over the next few months and be assessed for their ability to limit or modify SARS-CoV-2 infection. In addition, a drug that reliably prevented progression of COVID-19 would greatly reduce the concerns and uncertainty associated with SARS-CoV-2 infection and give physicians a therapeutic tool they must have for their patients. Establishing the therapeutic or prophylactic efficacy of monoclonal antibodies would be a major advance in the control of the COVID-19 pandemic.

ARTICLE INFORMATION

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