Review Article

CLINICAL INVESTIGATION

COVID-19 therapy with neutralising monoclonal antibodies

Abstract

Several neutralising Monoclonal Antibodies (mAbs) to the coronavirus that causes Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) have been produced and are currently being tested in clinical trials. Given the recent emergency use authorizations for neutralising mAbs in non-hospitalized patients with mild-to-moderate COVID-19 by the US Food and Drug Administration, there is an urgent need to discuss the broader potential of these novel therapies and develop strategies to effectively deploy them in clinical practise, given their limited initial availability. From the history of passive vaccination and the lessons learnt from employing antibody treatments to treat viral illnesses including respiratory syncytial virus, Ebola virus, and SARS-CoV. The use of convalescent plasma and neutralising mAbs for SARS-CoV-2 treatment is then discussed. For optimal clinical application, examine particular clinical problems such as the rationale for patient categorization, prospective biomarkers, known risk factors, and temporal considerations. To answer these questions, researchers must first comprehend factors such as viral load kinetics and their relationship to clinical outcomes, endogenous antibody responses, neutralising mAb pharmacokinetic properties, and the potential benefit of combining antibodies to defend against emerging viral variants.

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Introduction

Various preventative and therapeutic medicines are being developed or repurposed to tackle COVID-19 in the midst of the present pandemic. A new class of antiviral intervention is monoclonal antibodies (mAbs) that can bind to and 'neutralise' the virus in infected people. Neutralizing mAbs are recombinant proteins generated from convalescent patients' B cells or humanised mice's B cells. Antibodies with the required specificity and affinity to bind to a virus and inhibit entry of the virus can be identified through high-throughput screening of these B cells, eliminating the pathologies associated with productive infection [1-3]. These mAbs are known as 'neutralising' and they can be employed as a sort of passive immunotherapy to reduce virulence (more on that later). We analyse the function of neutralising mAbs among the spectrum of prospective COVID-19 therapies in this Review, highlighting the relative benefit that these medicines can bring for patients and physicians.

Three anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mAb therapies have received Emergency Use Authorization (EUA) in the United States for the treatment of non-hospitalized patients with mild-to-moderate COVID-19: bamlanivimab as a monotherapy, and bamlanivimab combined with etesevimab or casirivimab with imdevimab as a combination therapy. As a result, several questions about the potential clinical use of neutralising SARS-CoV-2 mAbs must be addressed, including: who should receive them; what is the best dose and frequency; when in the course of the infection will they be most effective; what is the duration of the protection they provide; and what is the associated benefit-to-risk ratio. Furthermore, neutralising mAbs could be used as a preventative measure in people who are at high risk of severe COVID-19 [4]. Indeed, preliminary data suggest that mAbs prevent COVID-19 in high-risk people who might be exposed to SARS-CoV-2 in nursing homes or at home. While vaccines are still the greatest way to prevent COVID-19, mAbs could help certain vulnerable populations before or after exposure to SARS-CoV-2, such as high-risk individuals who have never been vaccinated or who have recently been immunised. The antiviral activity found with neutralising mAb treatment underscores the significance of early intervention to help offset the virus's catastrophic impact in these and other high-risk patients. mAbs, on the other hand, are difficult to make and may have a limited initial supply. Furthermore, any protection

provided would be ephemeral, and the length of time that effective protection would last is unknown. As we explore here, answers to these issues will enable for the most effective application of these revolutionary and potentially life-saving medicines.

The first important breakthrough in modern immunological intervention was developed more than 125 years ago, a therapeutic serum derived from animals actively inoculated against diphtheria toxin 8,9. Later, Paul Ehrlich published a seminal paper linking curative antiserum to neutralising antibodies. Antigen-specific mAbs or polyclonal antibodies produced from non-human or human blood sources are now used in passive immunization [5]. While polyclonal antibodies derived from immunised animals are the most common source of antisera, there is a risk of 'serum sickness,' particularly after repeated exposures, because the receiver may develop an immunological reaction to non-human antibodies. The use of convalescent plasma from human patients reduces these hazards. Convalescent Plasma Treatment (CPT) can be effective with minimum safety hazards with proper screening (for example, to evaluate for the presence of infectious pathogens and to establish antibody titre and neutralizing capacity). CPT was used to treat illnesses caused by influenza virus, Respiratory Syncytial Virus (RSV), Ebola virus, and other coronaviruses prior to the current pandemic. CPT appears to be most effective when taken soon after symptoms develop, rather than during a severe or persistent infection. It may also offer protection to immune compromised or unvaccinated high-risk persons who have recently been exposed to infection. The use of plasma with higher neutralizing antibody titres has been linked to better clinical outcomes. Convalescent plasma, on the other hand, has a wide range of antibody titres. CPT is versatile and convenient for usage in resource-limited situations, and it can be quickly implemented to tackle new virus epidemics.

Anti-pathogen antibodies derived from convalescent plasma can protect against infection through two mechanisms: antibody effector activity and pathogen neutralisation. In rare situations, however, pathogen-specific antibodies can boost virulence through a process known as 'Antibody-Dependent Enhancement' (ADE). ADE can be caused by two different methods. First, pathogen-specific antibodies may promote virus uptake and replication in Fc receptor-expressing immune cells, thereby increasing infection (for example, as is seen in dengue hemorrhagic virus infection of macrophages). *In vitro* evidence suggests that the non-lymphotropic coronaviruses SARS-CoV and SARS-CoV-2 are unable to multiply effectively within hematopoietic cells [6,7]. ADE can also be caused by enhanced immune activation caused by Fc-mediated effector activities or the development of immunological complexes. The immunological cascade that results from respiratory viral infections can lead to lung disease. While the symptoms of severe COVID-19 are similar to those of this type of ADE, there is yet no conclusive proof that ADE occurs when SARS-CoV-2 infection is present.

Advantages of monoclonal antibodies

Replacement of CPT with neutralising mAbs is becoming increasingly popular, as dosage to guarantee optimal neutralising capacity of the antibodies may be more accurate. The technology for mass-producing recombinant mAbs has now become scalable and cost-competitive with alternative treatments. CPT's inherent limitations are overcome by neutralising mAbs (for example, the risk of blood-borne diseases, time to development of detectable high-affinity antibodies and risk of low antibody titres, as well as variable epitope specificity). Furthermore, neutralising mAbs have a high titre of neutralising antibodies, which is required for CPT efficacy according to current research. Palivizumab, a neutralising monoclonal antibody to the RSV fusion protein, was first approved in 1998 as a prophylactic treatment for severe RSV infection in high-risk newborns. Previously, monthly infusions of RSV immune globulin were the standard of therapy for prevention in these individuals. Palivizumab was well tolerated when given monthly intramuscular injections and reduced the incidence of hospitalisation and severity of RSV disease compared to placebo. Palivizumab, on the other hand, has not been shown in RCTs to enhance clinically relevant outcomes in infants with severe RSV infection in advanced stages of disease. Furthermore, to maintain detectable levels of neutralising mAbs, monthly injection is required, and up to five doses may be required to avoid severe or fatal infection. A newer medicine (MEDI8897) with a longer half-life is currently being tested in phase II/III trials.

Conclusion

During the Ebola virus disease outbreak in the Democratic Republic of the Congo in 2018, an open-label RCT (PALM) looked at four intravenously administered treatments in 681 Ebola patients: the antiviral remdesivir, the triple mAb cocktail ZMapp, the single mAb MAb114, and the triple mAb combination REGN-EB3. The first two therapies were terminated after an interim analysis revealed that MAb114 monotherapy and REGN-EB3 were superior in terms of the primary endpoint, patient death. One possible explanation provided by the PALM study team for the difference in the therapies is that the entire treatments for MAb114 and REGN-EB3 were given as a single dosage, allowing for a faster response, whereas ZMapp was given as three infusions. The fact that patients treated with MAb114 and REGN-EB3 exhibited faster viral clearance rates backs up this theory. Overall, those who were treated early at symptom onset and had lower baseline virus loads had a better chance of surviving. The ZMapp triple cocktail's low efficacy also serves as a reminder that the amount of mAbs used isn't always a good predictor of efficacy and that epitopes matter as well. Passive immunisation still has major unknowns, one for neutralising mAbs and the other for CPT. First, how might their usage as a preventative or treatment effect long-term immunity? Given the high quantities utilised and the short half-life of antibodies (three

weeks for IgG molecules), it's worth asking if the presence of circulating neutralising mAbs could affect active immunity, whether through infection memory or vaccination. In RSV infection, rodent and primate infection models show that passive antibody transfer slows the development of humoral immunity in the recipient. Yet, long-term memory was enough to protect the hosts from reinfection, thanks to an intact T cell memory compartment. Given the difficulties in interpreting data from animal models (where RSV replication is reduced compared to that in its human host), further data, particularly from clinical trials, will be crucial in addressing this possible problem.

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