REVIEW

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Antibody therapy for COVID-19

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Purpose of review
To provide an update of the current state of antibody therapy for Severe Acute Respiratory Syndrome Coronavirus 2 infection that has progressed immensely in a very short time period.

Recent findings
Limited clinical effect of classical passive immunotherapy (plasma therapy, hyperimmune immunoglobulin [IgG] preparations) whereas monoclonal antibody therapy, if initiated early in the disease process, shows promising results.

Summary
Although antibody therapy still remains to be fully explored in patients with COVID-19, a combination of IgG monoclonal antibodies against the receptor-binding domain of the spike protein currently appears to provide the best form of antibody therapy, Immunoglobulin A dimers and Immunoglobulin M pentamers also show promising preliminary therapeutic results.

Keywords
COVID-19, hyperimmunoglobulin, monoclonal antibodies, plasma therapy

INTRODUCTION

Passive immunization has, for more than a century, proven to be highly efficient for treatment and prevention of infectious diseases, particularly in individuals suffering from immunodeficiency, or individuals in whom vaccination is contraindicated. Passive immunization may thus represent a suitable therapy in global emergency situations where vaccines are lacking or where the populations at risk have not been fully vaccinated (for review see [1]).

The immunoglobulin (IgG) preparations used for passive immunization are generally purified from human sera with high titers against the microorganisms (following natural infection or vaccination), either as single donations used for plasma therapy or pooled plasma but may also include human/humanized monoclonal antibodies or even sera from animals. Furthermore, the most commonly recommended form of treatment for primary immunodeficiency disorders is replacement therapy with intravenous or subcutaneous gamma globulins (IVIG or SCIG) from healthy human donors. In the past few years, a large number of broader and potent neutralizing monoclonal antibodies have also been isolated, some of which are already in clinical trials/clinical use.

Today's renewed interest in antibody therapies is the consequence of major advances in the technology of antibody development combined with the need for new therapeutic agents against emerging diseases (Ebola, ZIKA, SARS, bird flu, West Nile virus, bioterrorism agents) and new antibiotic resistant microorganisms (Staphylococcus *aureus*, *Enterobacteriaceae*, Enterococci, Clostridium *difficile*). Passive immunization using polyclonal or monoclonal antibody preparation may also be a potential solution for control of current or future pandemics. This review will focus on antibody-based therapies aimed at treating or mitigating infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

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KEY POINTS

- Antibodies against SARS-CoV-2 have already been used extensively as therapy against COVID-19 during the current pandemic.
- Several combinations of monoclonal IgG antibodies have been approved for emergency use in severely affected patients whereas the use of a single monoclonal antibody is discouraged owing to the risk of development of viral escape mutants.
- Further research is needed to understand the potential role of autoantibodies against interferon, contained in some plasma preparations derived from convalescent donors, in the variable clinical results obtained in patients infused with plasma or plasma-derived products.

ANTIBODIES AGAINST SARS-CoV-2 IN COMMERCIAL STANDARD GAMMAGLOBULIN PREPARATIONS

As SARS-CoV-2 is a novel coronavirus, there is no prior immunity against this pathogen in the population. Thus, as expected, plasma collected before 2020 does not contain any specific antibodies against the virus [2], nor is there any protective crossreactivity afforded by antibodies against related coronaviruses in these plasma donations. However, starting in the autumn of 2020, the pools of plasma collected for fractionation and production of gammaglobulin preparations started to show positive antibody titers. From then on, levels of specific anti-SARS-CoV-2 antibodies have risen steadily and by the summer of 2021, the levels are expected to be at par with those seen in convalescent plasma used for treatment of patients with COVID-19 [3,4]. Owing to the quarantine requirements, there is a 6–12 months time lag before the collected plasma may be fractionated and made available for therapeutic purposes. With time, these preparations would also be expected to, depending on the geographical origin of the plasma, contain antibodies against the newly emerging virus variants and thus be suitable for prophylaxis or even therapy against SARS-CoV-2.

THE RISE AND FALL OF CONVALESCENT PLASMA THERAPY TO COMBAT SARS-CoV-2 INFECTION

Bearing in mind the historical successful use of convalescent plasma therapy in combating infections, it was early on during the pandemic being considered as a potential therapeutic option for treatment of severely ill COVID-19 patients. Plasma obtained from convalescent donors has previously been used as a therapy against Coronavirus infections, including 80 patients in Hong Kong, infected with SARS-CoV-1 during the 2003 outbreak (resulting in a reported lower mortality rate (12.5%) compared with nonplasma treated patients (17%) [5]. Similarly, Yeh *et al.* treated three patients with a severe clinical condition using two doses of 500 ml plasma, resulting in a rapid reduction/elimination of virus in blood and survival of the patients [6]. Antibody therapy was also suggested during the Middle East respiratory syndrome (MERS) outbreak [7] but not attempted in patients although a number of animal studies suggested a therapeutic effect of convalescent plasma, hyperimmune IgGs (from animal sources) and monoclonal antibodies.

Plasma therapy in small noncontrolled series of patients with severe SARS-CoV-2 infection [8–12] was initially reported to show beneficial effects. Some subsequent reports (a total of more than 1500 articles in PubMed using the search term plasma therapy COVID-19) also claimed therapeutic results [13,14▪,15]. However, some randomized studies have not supported the initial claims [16,17]. Recent meta-analyses, summarizing large studies with more than 10 000 patients, has concluded that there is in fact no positive effect of convalescent plasma in COVID-19 patients with severe disease [18,19▪▪,20]. The differing results suggest that factors hitherto not fully accounted for, including content and quality/class of the neutralizing anti-SARS-CoV-2 antibodies, timing of the therapy, the volume of plasma used and the content of anti-IFN antibodies in the individual plasma donations (see discussion), may have led to discrepant therapeutic results. On the other hand, growing evidence support the use of plasma therapy in immunocompromised individuals, especially those receiving B cells depleting drugs such as Rituximab [21–23]. All in all, convalescent plasma therapy is difficult to standardize and its role may be restricted to the early epidemic phase, characterized by limited therapeutic options or specific patient groups.

DEVELOPMENT OF A HYPERIMMUNE ANTIBODY PREPARATION

As titers of anti-SARS-CoV-2 antibodies may vary considerably between the plasma donors, resulting in differences in therapeutic efficacy, manufacturing of a hyperimmune IgG would allow standardization of treatment. We initially planned a project on fractionation of plasma from convalescent donors from Wuhan, China, the very center of the pandemic. This was the only region in the world where a significant number of convalescent donors was available in the early stages of the pandemic. However, collecting

the required volume of plasma turned out to be an unsurmountable logistic feat owing to the local lockdown in Wuhan and our initiative was terminated. Our commercial partner, however, brought the project forward by joining forces with several other gammaglobulin producing companies (CSL Behring, Takeda, Biotest, BioPharma PlasmaGC Pharma, Octapharma, LFB and Sanquin) in an unprecedented collaborative effort. The joint group, the Plasma Alliance, managed to collect enough starting material and the resulting product, CoVIg, made it possible to design and carry out a global, multicenter, double-blind, placebo-controlled, randomized clinical trial - Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) on a large number of patients, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The study was initiated in the autumn of 2020 and the adult patients ($n = 594$) were all given Remdesivir and either the hyperimmune IgG preparation or placebo.

The preliminary results of this ambitious study were reported in early summer this year (News release from the Takeda company on April 2nd, 2021: CoVIg-19 Plasma Alliance Announces Topline Results from NIH-Sponsored Clinical Trial of Investigational COVID-19 Hyperimmune Globulin Medicine) and unfortunately showed no therapeutic effect of the antibodies. The full report on the trial is anticipated in the early autumn.

The immune response against SARS-CoV-2 in infected individuals follows the normal pattern with initial production of Immunoglobulin M (IgM) antibodies followed by IgG and Immunoglobulin A (IgA) with continuous affinity maturation of the antibodies where IgA may in fact dominate the early response. The titers of antibodies of the IgM and IgA diminish within a month although the latter may be present in saliva for a for a slightly longer time [24]. Levels of IgG remain for a markedly extended period [25,26] as is also the case with antibodies against other Coronaviruses including SARS-CoV and MERS [27]. Although the IgG antibodies may persist for many years, it remains to be shown how long the protective anti SARS-CoV-2 response will ultimately last.

THE USE OF MONOCLONAL ANTIBODIES FOR THERAPY AGAINST SARS-CoV-2

The early antibody response is dominated by IgA (of the IgA1 subclass), which appears before IgG and contributes to a greater extent to the virus neutralization at mucosal sites in the initial stages of infection [24]. The superiority of the monomeric IgA molecule as compared to IgG may be due to its increased flexibility and its longer hinge region, allowing a more favorable spatial interaction with the spike protein. Dimeric IgA, the molecular form at mucosal surfaces, was subsequently shown to be more potent than the monomeric form both in terms of binding and neutralizing capacity [28▪▪]. Finally, a genetically engineered monoclonal antibody with a Fv portion of an IgG antibody was grafted into human IgM and IgA scaffolds where the IgM was expressed as a pentamer and the IgA1 as a dimer. Again, the dimeric IgA molecule showed superior activity as compared to its IgG parent antibody but the IgM was vastly more effective in terms of binding and neutralization and showed a potent prophylactic and therapeutic effect when applied intranasally in mice [29]. Yet another alternative that has received attention for the past years is the use of camelid Variable region of heavy chain only antibodies (nanobodies9 from camelids) (VHH) fragments (nanobodies) which may recognize epitopes that are often inaccessible to conventional antibodies. Thus, Xu *et al.* isolated anti-RBD nanobodies from alpacas, dromedaries and camels, some of which targeted a highly conserved epitope in coronaviruses, rarely recognized by human antibodies, and one set of nanobodies which was highly neutralizing even against recently emerging virus variants when expressed as a homotrimer [30▪]. The above observations may have a profound impact on the choice of antibody class/molecular form of monoclonal antibodies for human therapy.

Several monoclonal antibodies against SARS-CoV-2 have been developed, following the successful production of human/humanized monoclonal antibodies against other recently emerging infections, including Zika [31,32] and Ebola [33,34]. Some of the monoclonal antibodies previously raised against SARS-CoV-1 have shown cross-reactivity against SARS-CoV-2 [35] and a large number of novel monoclonal antibodies, mainly of the IgG class, against the new virus have also been generated with an astonishing speed and are continuously being added to the therapeutic arsenal (for review see [36▪▪]).

Three monoclonal antibody preparations against SARS-CoV-2 are currently available for treatment of patients with mild-to-moderate COVID-19 infections. Bamlanivimab (LY-CoV555) from Eli Lilly was initially used as a monotherapy in 452 patients as a single infusion in three different doses [37▪] where the rate of emergency visit or hospitalization was reduced from 6.3% in the placebo group to 1.6% in the combined treatment group. However, owing partly to the risk for emergence of viral escape mutants, etesivimab was later added to the product (2800 mg of each monoclonal antibody) and tested in 1035 infected adults [38▪] with 518 receiving a single infusion of the combination of monoclonal antibodies. These two antibodies bind to different

but overlapping sites on the spike protein of the virus and resulted in a reduction in COVID-19 related hospitalization or death from 7% to 2% where all the deaths occurred in the placebo group.

Two other monoclonal IgG antibodies, casirivimab and imdevimab, developed by Regeneron and targeting nonoverlapping epitopes in the receptor-binding domain of the spike protein have also been used successfully in clinical trials. The use of an equal mixture of the antibodies was made to reduce the risk for development of escape mutants. A preliminary report on 275 nonhospitalized patients [39▪] showed a decreased viral load from baseline through day 7 after treatment with a greater effect in patients who were seronegative at the start of therapy, i.e., in the very early stages of infection. Subsequently, a study based on 9785 patients hospitalized with COVID-19 was reported recently [40] using a single dose of 8 g of antibodies (4 g of each) where the primary outcome was 28-day mortality. In the population of seronegative patients, 396 (24%) of the treated patients died whereas 451 (30%) of the patients receiving usual care died within the 28 days period ($P = 0.001$). In an analysis involving all randomized patients (regardless of baseline antibody status), no difference in mortality between the groups was observed, again emphasizing the crucial importance of early initiation of treatment.

On May 26, 2021, yet another anti-SARS-CoV-2 monoclonal IgG antibody, sotrovimab, originally isolated from a SARS infected patient in 2003, received FDA emergency use authorization based on an unpublished study on 291 patients with a reduced rate of hospitalization or death compared to placebo (1% as compared to 7%).

All anti-SARS-CoV-2 monoclonal antibodies previously or currently authorized for clinical use are restricted to patients with mild or moderate disease who are at a high risk for progression to severe COVID-19, thus limiting their clinical utility. Patients with a severe disease do not benefit from treatment with the above monoclonal antibodies that emphasize the notion that antibody-based therapy should be initiated early in the infectious process. This also has implications for potential treatment of immunocompromised patients with persistent SARS-CoV-2 infections.

It is apparent that monotherapy with monoclonal anti-SARS-CoV-2 antibodies is associated with a high risk for the appearance of viral escape mutants and the emergency use authorization for treatment with bamlanivimab was revoked by the U.S. FDA in April 2021. Meanwhile, the emergence of multiple SARS-CoV-2 variants-of-concern (VOCs) with mutations in the spike Receptor binding domain (RBD) an challenging the neutralizing serum-activity have been reported.

Thus, a cocktail of two separate antibodies is strongly preferred. One alternative approach was recently published [41▪▪] where a bispecific antibody, formed by two human IgG monoclonal antibodies which bind to independent sites on the RBD of the spike protein. This bispecific antibody protects SARS-CoV-2 infected mice from disease and suppressed viral escape and combines the advantages of antibody cocktails with those of single molecule approaches.

This part of our review has focused on antibodies against the SARS-CoV-2 virus itself and it should be recognized that many additional therapeutic monoclonal antibodies have also been developed that target molecules involved in the regulation of the immune response or proinflammatory cytokines contributing to the progress of the disease.

DISCUSSION

Passive immunotherapy is a century old treatment modality that has been successfully used both for oral and systemic administration against bacterial and viral infections. It is therefore somewhat surprising that therapy against SARS-CoV-2 using convalescent plasma and hyper IgG has largely failed, in spite of massive efforts. A contributing factor could be the varying titers of neutralizing antibodies in the individual convalescent plasma donations. However, the latter would not apply to the CoVIg hyperimmune preparation used in the ITAC study, suggesting that other factors such as timing of the start of treatment, may underly the encountered treatment failures.

Patients infected with SARS-CoV-2 develop a wide variety of autoantibodies including type I Interferons, mainly but not limited to IFNα and IFNw [42▪▪], Angiotensin converting enzyme 2 [43], chemokines and complement components [44▪▪]. In some cases, the antiinterferon antibodies have been shown to be present before the infection and associated with a high mortality rate [42▪▪]. In view of the critical importance of Interferons in combating the infection, as shown by the high risk for severe disease in patients with Inborn Errors of Immunity involving the interferon system [45], it is possible that the presence of these autoantibodies in some of the plasma donations contain antiinterferon antibodies which, when infused, will inhibit endogenous interferon production in the patient and thus influence the clinical outcome.

Only a small proportion of patients with mild or moderate SARS-CoV-2 infection will progress to severe disease and thus, although large numbers of patients

have been enrolled in the clinical trials to date, the number of infected individuals who benefit from the treatment is rather low. The key is to identify markers (genetic or biochemical) that would rapidly predict the risk for progressive disease in the individual patient in order to avoid excessive treatment costs, an important issue in low-or-middle income countries. Vaccination would probably be a more cost-effective regime but until sufficient coverage in the general population has been reached, monoclonal antibodies will still provide an important therapeutic tool, particularly in patients failing vaccination because of inborn errors of immunity or iatrogenically immunocompromised individuals.

CONCLUSION

Passive immunization using preformed antibodies is a more than a century old therapeutic method for selected infectious diseases. Various approaches, including plasma therapy, hyper IgG and monoclonal antibodies have been used to try to combat the COVID-19 pandemic. The former two methods have achieved limited positive clinical results whereas combinations of monoclonal antibodies show clinical efficacy if administered early in the disease process. Future research within this field should thus be aimed at trying to optimize the composition of the antibody preparations.

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Conflicts of interest

There are no conflicts of interest.

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