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Neutralizing antibodies for SARS-CoV-2 infection

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ABSTRACT

The COVID-19 pandemic has boosted significant research in developing monoclonal antibodies (mAbs) to treat and prevent SARS-CoV-2 infection. Clinical trials have shown that mAbs are safe and effective in preventing hospitalization and death in patients with mild to moderate COVID-19 risk factors for progression. mAbs have also been effective for treating severe disease in seronegative patients and preventing COVID-19. So far, studies have been carried out in a largely unvaccinated population at a time when the omicron variant was not described. Future research should address these limitations and provide information on specific population groups, including immunosuppressed and previously infected individuals.

Keywords: Covid-19, SARS-CoV-2, coronavirus, monoclonal antibody.

INTRODUCTION

The use of serum therapy in medicine was initiated by Behring and Kitasato in 1890 with the development of diphtheria antitoxin. Many decades later, the development of monoclonal antibodies (mAbs), derived from a single B lymphocyte clone that recognizes one and only one specific epitope, was a major medical breakthrough. The first mAb used in clinical practice was Muronomab, an anti-CD3 antibody approved in 1975 by the Food and Drug Administration (FDA) for preventing kidney transplant rejection. The first mAb in Infectious Diseases therapeutics was Palivizumab, approved in 1998 to prevent severe respiratory syncytial virus (RSV) disease in high-risk children. Later, other mAbs for anthrax, rabies, HIV, and Ebola were marketed or approved for conditional emergency use [1].

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The mechanism of action of mAbs in viral infections is multiple. It includes the direct binding of the antibody's antigen binding site to free viral particles, neutralizing its ability to infect host cells. In addition, the fragment crystallizable (Fc) region of the antibody stimulates opsonization, antibody-dependent phagocytosis, and antibody-dependent and complement-dependent cytotoxicity [2].

Over the last two years, the COVID-19 pandemic has boosted significant research in developing mAbs against SARS-CoV-2. Clinical Trials have been developed for early treatment in patients with mild/moderate disease at risk of progression to severe/critical disease and late-stage treatment in patients with severe or critical illness. Here we will review the clinical experience of mAbs in these two scenarios. It should be noted that studies with mAbs for SARS-CoV-2 pre-exposure prophylaxis and post-exposure prophylaxis are also being carried out [1].

MONOCLONAL ANTIBODIES AGAINST SARS-COV-2

The SARS-CoV-2 particle is surrounded by the spike protein integrated by three monomers, one of which is the receptor binding domain (RBD), that contacts the angiotensin-converting enzyme 2 (ACE2) receptor in the host cell through the receptor binding motif (RBM), its functional site [3,4]. The RBD is the main target of mAbs against SARS-CoV-2, some of which bind directly to the RBM [5,6]. mAbs against SARS-CoV-2 are classified based on their target RBD antigenic sites [1]. There are currently four classes of monoclonal antibodies that bind to four different sites, some of which are more mutable than others. Mutations in the RBD of the different viral variants can affect the antiviral activity of mAbs against SARS-CoV-2. The activity of mAbs against the different SARS-CoV-2 variants is regularly updated on the Stanford University Coronavirus resistance database [7]. Besides, the National Institute of Health (NIH) guidelines also review the activity of the different mAbs

Table 1 **Efficacy of monoclonal antibodies against SARS-CoV-2 in non-hospitalized patients with COVID-19. Modified from reference 9**

	Bamlanivimab Etesivimab	Casirivimab Imdevimab 2400	Casirivimab Imdevimab 1200	Sotrovimab	Tixagevimab Cilgavimab	Regdanvimab
Administration Route	Intravenous	Intravenous	Intravenous	Intravenous	Intramuscular	Intravenous
Clinical trial name	BLAZE-1	na	na	COMET-ICE	TACKLE	CT-P59 3.2
Hospitalizations in mAb group	11/518 (2.1%)	18/1355 (1.3%)	7/736 (1.0%)	3/291 (1.0%)	18/407 (4.4%)	16/656 (2.4%)
Hospitalizations in PLBO group	36/517 (7.0%)	62/1341 (4.6%)	24/748 (3.2%)	21/292 (7.0%)	37/415 (8.9%)	53/659 (8.0%)
% Reduction in hospitalization or death	70.0	71.3	70.4	85.0	50.0	70.0
Number needed to treat	21	30	44	16	22	18

authorized by the FDA [8]. Of note, the neutralizing activity against the omicron variant is significantly reduced for all mAbs except for sotrovimab; an antibody derived from a patient infected with SARS-CoV-1 in 2003 that binds to a highly conserved region of the spike protein away from the RBD.

MONOCLONAL ANTIBODIES AGAINST SARS-COV-2 IN OUTPATIENTS

The information we have on the main pivotal clinical trials with mAbs for the treatment of COVID-19 in outpatients is summarized in Table 1 [9]. All these studies have been carried out in a largely unvaccinated population and, more importantly, at a time when the omicron variant was not described.

Given that sotrovimab is the only mAb active in vitro against the omicron variant, it is worth noting the phase III COMET-ICE clinical trial whose pre-specified interim analysis was published in November 2021 when approximately 40% of the patients had been included [10], and whose final results were communicated in September 2021 in the IDWeek 2021 meeting [11] (Table 2). This clinical trial evaluated the efficacy and safety of sotrovimab in outpatients with mild to moderate COVID-19 at risk of progression to severe COVID. Patients were randomized to sotrovimab 500 mg IV or a dose of placebo. The primary outcome variable was admission or death from any cause in the first 29 days. Patient characteristics were well distributed between groups; 54% were women, the median age was 53, and 87% were white. The duration of symptoms was three days or less in 59%, and the most frequent risk factors for progression were obesity, age greater than or equal to 55 years, and diabetes mellitus. Regarding the primary efficacy analysis, there was hospitalization or death at 29 days in six patients in the sotrovimab group (1.1%) and 30 in the PBO group (5.7%), representing a 79% reduction in the risk of hospitalization or death using sotrovimab. In a post-hoc review, it was found that three of the six admissions in the sotrovimab group were not related to COVID-19: lung cancer, diabetic foot, and intestinal obstruction, while the 30 in the placebo group were related to COVID-19 (29 admissions and one death). Concerning the secondary efficacy outcomes, it should be noted that sotrovimab therapy was associated with a 66% reduction in visits to the emergency department, a 74% reduction in the development of severe or critical illness, and that there were no deaths in this arm while there were two in the placebo group.

MONOCLONAL ANTIBODIES AGAINST SARS-COV-2 IN HOSPITALIZED PATIENTS

The first data about mAb treatment of severe COVID-19 in hospitalized patients were generated on the RECOVERY platform in the United Kingdom, where almost 10,000 patients hospitalized for COVID-19 between September 2020 and May 2021 were randomized 1:1 to the combination of casirivimab with imdevimab (CAS/IMD) or standard treatment [12]. The mean patients age was 62 years, the median time from symptom onset to randomization was nine days, 94% of patients were receiving corticosteroids as part of the standard of care, and 32% had negative serology for SARS-CoV-2. Between 50% and 60% of the patients had some underlying disease, the predominant ones being diabetes, heart disease, and chronic lung disease. The risk of death at 28 days, hospital discharge alive, and need for mechanical ventilation or death were not significantly different between the two groups. However, when a stratified analysis was made according to the SARS-CoV-2 serology result, it was observed that treatment with CAS/IMD provided clear benefits in terms of lower mortality, higher probability of survival, and lower risk of mechanical ventilation. Or death. The number needed to treat (NNT) was 16.7 to prevent one death, 16.7 to be discharged alive, and 14.3 to prevent mechanical ventilation or death.

CAS/IMD was also studied in a randomized, double-blind clinical reported as Late Breaker at the IDWeek 2021 meeting [13]. The inclusion criteria were hospitalization due to COVID with no more than three days of admission and duration of symptoms of no more than ten days. Patients were randomized 1:1:1 to two doses of CAS/IMD or placebo, stratified by the COVID treatment they received: nothing, remdesivir (RDV), corticosteroids, or RDV + corticosteroids. The clinical trial contemplated two primary outcome variables: a virological one (change in viral load from baseline to day 7 in seronegatives)

Table 2 **Efficacy of monoclonal antibodies against SARS-CoV-2 in non-hospitalized patients with COVID-19. Modified from Reference 11**

Outcome	Sotrovimab (n=528)	Placebo (n=529)	Relative risk ratio (95% CI)	P
Primary outcome				
Hospitalization for > 24 h for acute management of illness or death through day 29, No. (%)	6 (0.2)	30 (5.7)	0.21 (0.09 - 0.50)	<0.001
Selected secondary outcomes (through day 29)				
Emergency room visit, hospitalization, or death due to any cause, No. (%)	13 (2)	39 (7)	0.34 (0.19 - 0.63)	<0.001
Progression to severe/critical respiratory COVID-19, No. (%)	7 (1)	28 (5)	0.26 (0.12 - 0.59)	0.002
All-cause mortality, No. (%)	0	2 (<1)		

and a clinical one (death or mechanical ventilation on day 29). CAS/IMD was superior to placebo considering the two outcome variables: virological and clinical, with a relative risk reduction of mechanical ventilation or death at 29 days of 47% in the seronegative group and with an NNT of 11.

A clinical trial by the Therapeutics for Inpatients with COVID-19 Study Group (TICO) has recently been published in which the efficacy of two mAbs was compared in patients hospitalized for COVID-19: sotrovimab and the combination of Amubarvimab/romlusevimab two derivative mAbs of a convalescent COVID-19 patient [14]. Recruitment took place between December 2020 and March 2021 in multiple countries, and the primary efficacy endpoint was time to clinical recovery after a 90-day follow-up. Complete clinical recovery was defined as being discharged home for at least two weeks. A total of 546 patients were enrolled and randomized 1:1:1 to placebo, Sotrovimab, or the combination of amubarvimab/romlusevimab. The patients included had a median age of 61 years, with a slight predominance of women, and approximately 75% of the patients had some underlying disease such as hypertension, diabetes, and less frequently kidney failure, asthma, and heart failure. Of note, approximately one-third of patients were seronegative for SARS-CoV-2. Recruitment was terminated after a protocol-specified interim analysis showed no change in an ordinal scale of lung involvement. Furthermore, neither active treatment arm significantly shortened the time to clinical improvement compared to the placebo. No signal was observed in terms of mortality either, with 14 (8%) dying in the sotrovimab group, 13 (7%) in the placebo group, and 15 (9%) in the amubarvimab/romlusevimab group.

CONCLUSIONS

mAbs treatments are safe and effective in preventing hospitalization and death in patients with mild to moderate COVID-19 risk factors for progression. They also have the potential for the treatment of severe COVID-19 in seronegative patients and as preventive tools against COVID-19. We need more information on the efficacy of mAbs against some variants (omicron) and in some groups of patients (immunosuppressed, vaccinated, previously infected).

CONFLICT OF INTERESTS

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