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## Update in SARS–CoV–2 pneumonia

Rosario Menéndez[1]
Paula Gonzalez[1,2]
Ana Latorre[2]
Raúl Méndez[1,2]

# Immune treatment in COVID-19

[1]Pneumology Department, La Fe University and Polytechnic Hospital, Valencia Spain. Spanish Society of Pneumology and Thoracic Surgery (SEPAR)
[2]Respiratory Infections Research Group, Health Research Institute La Fe, Valencia Spain.

## ABSTRACT

Current immune treatment directed to avoid viral replication relies mainly in convalescent plasma and monoclonal antibodies (mAbs). No clinical benefit for convalescent plasma has been reported in a meta-analysis and systematic review compared to standard of care. MAbs are recombinant proteins capable to bind with SARS-CoV-2 preventing its entrance into cells. Several mAbs have shown reduction in viral load and/or progression of the disease such as casirivimab-imdevimab, bamlanivimab-etesevimab and sotrovimab. After the apparition of Omicron variant, it has been reported that sotrovimab retained its activity whereas the other two combinations exhibited loss of neutralizing activity. Several aspects as the target population, timing and doses, serological patient status and evolution of variants still require attention, monitorization and further studies for knowledge gaps.

Key words: monoclonal antibodies, S protein, SARS–CoV–2

## INTRODUCTION

During the whole pandemic and the successive waves some differences among the patient profile have been reported. Nevertheless, it was rather constant that patients with immunosuppression, elderly and those with several risk factors for progression are still a vulnerable group with difficulties to mount an effective immune response causing a challenge for treatment (Table 1). For so, despite the high proportion of vaccinated, health resources are still compromised and a large amount of people would require hospitalization and even admission to ICU [1]. Concerning the microorganism it is crucial for clinical course and outcome the viral load and persistence of replication therefore a treatment directed to avoid virus-es entering into cells host constitutes a new approach. In that clinical scenario, the ability to provide an immune treatment is a logical and attractive option. The two most studied options are: convalescent plasma and monoclonal antibodies (mAbs).

## CONVALESCENT PLASMA

In a randomized trial performed, Estcourt [2] evaluated in two arms (convalescent plasma vs. Placebo) in critically ill patients. The primary ordinal end point was organ support-free days (days alive and free of intensive care unit-based organ support) up to day 21. The results showed neither no differences for primary outcome nor for mortality that was very high in the two arms (37.3% vs 38.4%). Janiaud et al [3] in a systematic review including 1060 patients from 4 peer-reviewed RCTs and 10,722 patients from 6 other publicly available RCTs. They concluded that convalescent plasma showed no benefit for all-cause of mortality and other outcomes as deterioration or requirement of mechanical ventilation.

## MONOCLONAL ANTIBODIES

Neutralizing monoclonal antibodies (mAbs) against SARS-CoV-2 are recombinant proteins obtained from B cells of patients or humanized mice. MAbs can be produced by different methods and constitute a method to provide passive immunization to patients. They act binding to virus and avoiding its fusion with ACE receptor – found on cells in the respiratory system, gastrointestinal tract and endothelium- neutralizing its capacity to enter into the host 'cells. The primary antigenic epitope on SARS-CoV and SARS-CoV-2 is the S protein and specifically receptor-binding domain (RBD) in most of them. Moreover, after binding with viruses facilitate the cellular phagocytosis and antibody-dependent cellular cytotoxicity directly or in infected cells promoting eventually their apoptosis [4]. A potential problem is that mAbs might cause damage through antibody-dependent enhancement of inflammation or viral replication.

Correspondence:
Rosario Menéndez
Pneumology Department, La Fe University and Polytechnic Hospital, Valencia Spain.
E-mail: rosmenend@gmail.com

**Figure 1** | Graph representing the two phases –viral and inflammatory– in COVID–19 disease.
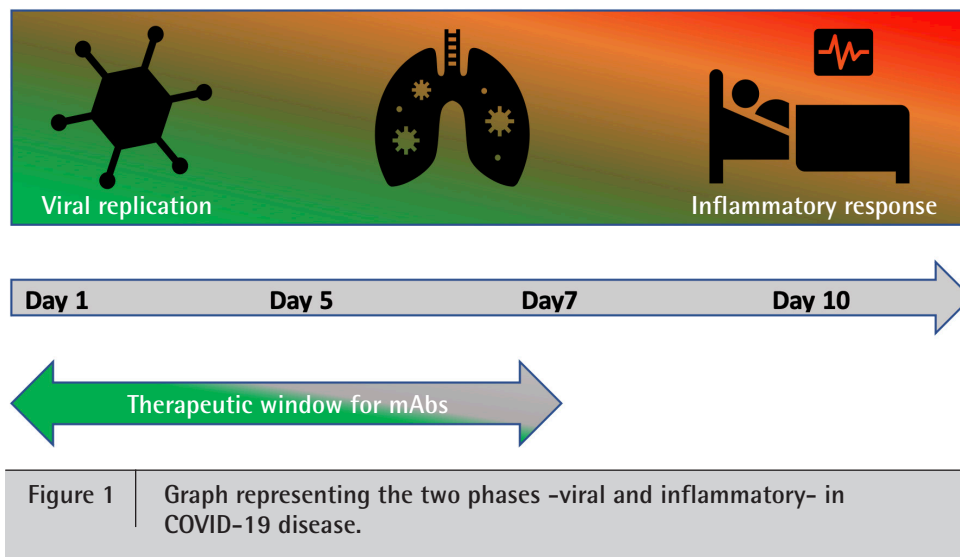
Due to their action mechanism mAbs as neutralizing antibodies are capable to reduce viral load when given in the early phase of viral replication precluding a disease progression through a clearance of viruses (Figure 1). The FDA, in United States and the EMA, in European countries have issued advice for the use of several mAbs, bamlanivimab and etesevimab, casirivimab and imdevimab (REGN-COV2) in outpatients who are not needing supplemental oxygen and who are at high risk of progressing severe COVID-19 and, lately, sotrovimab. The concern regarding mAbs from the initial studies was the potential loss of activity with the apparition of new variants with mutations precluding its binding to the S protein with the subsequent absence of efficacy [5].

**Bamlanivimab and etesevimab.** They are two humanized Ig G1 neutralizing antibodies that act against RBD. bamlanivimab-etesevimab bind to distinct although overlapping epitopes. In February 2021, Gotblier et al [6] compared the efficacy of bamlanivimab in monotherapy with different doses, or in combination with etesevimab and versus placebo in outpatients with mild or moderate COVID-19 (Blaze 1 study) to reduce viral virus load. Treatment was initiated within 3 days of SARS-CoV-2 positive test. They found that combination therapy, but not bamlanivimab monotherapy, resulted in a decrease in SARS-CoV-2 log viral load at day 11.

In July 2021, Dougan et al. [7] in a randomized 1:1 phase III trial performed in adolescent and adult nonhospitalized patients with mild infection and with at least one risk factor for progression, compared one infusion of mAbs (2,800 mg of bamlanivimab and 2,800 mg of etesevimab) vs. placebo. Treatment was administered within the first 4 days from onset symptoms and patients had a median Ct (cycle-threshold) of 23.9 the day of infusion. They found a significant lower hospitalizations and deaths at day 28 in the arm of treatment (70% reduction) and a rapid decline of viral load at day 11. During the trial, variants Beta o gamma were not observed. Poste-

rior studies have shown that some circulating viral variants, such beta and gamma variant have *in vitro* resistance to bamlanivimab plus etesevimab and it has been shown that is not active against Omicron variant [8].

**Casirivimab and imdevimab (REGEN–COV2).** RE-GEN-COV2 [9] is a combination of two neutralizing mAbs, casirivimab and imdevimab, formed with IgG1 with unmodified Fc regions that bind two distinct epitopes sites on RBD. In animal models, the combination reduced the viral load and the apparition of lung severe disease. Weinreich et al, in a phase III trial performed in outpatients with risk factors for progression, compared two different REGEN-COV iv doses (2,400 mg-1,200 mg casirivimab and 1,200 imdevimab- or 8,000 mg-4,000 mg of each) versus placebo. Patients were randomized to receive one of the two doses or placebo. This trial showed that REGEN-COV2 is associated with clinical benefit, regardless of baseline serum antibody status, so that serologic testing at the time of the COVID-19 diagnosis is less critical for making clinical treatment decisions. Both the 1,200 mg and 2,400 mg doses of REGEN-COV2 exhibited similar antiviral and clinical efficacy suggesting that REGEN-COV2 concentrations were above the minimally effective dose. Regarding adverse events, they reported low incidences of serious events, hypersensitivity reactions, and infusion-related reactions.

Noteworthy, the study revealed an association between the baseline viral load and COVID-19–related hospitalization or death in the placebo arm. In fact, seronegative antibody patients in the placebo group had higher median viral loads at baseline than those who were positive.

The 2,400 mg dose of REGEN-COV2 received an emergency use authorization from the FDA (Food and Drug Administration) in November 2020 for the treatment of high-risk outpatients with mild-to-moderate COVID-19. In June 2021, after this trial showed that the 1,200 mg dose provided a similar

| Table 1 | Eligible candidates for mAbs considering age ≥12 years and weight ≥40 Kg |
|---------|---------------------------------------------------------------------------|
| Age | ≥65 years |
| Immunosuppressed patients | Active treatment for solid tumor and hematologic malignancies |
| | Receipt of solid-organ transplant and taking immunosuppressive therapy |
| | Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant |
| | Moderate or severe primary immunodeficiency |
| | Advanced or untreated HIV infection |
| | Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive. |
| Chronic conditions | Cardiovascular disease and/or Hypertension |
| | Chronic renal disease |
| | Respiratory chronic conditions |
| | Cystic fibrosis |
| | Neurological conditions |
| | Sickle cell disease |
| Obesity | BMI >35 |
| | Overweight > percentile 85 |
| Technology dependence | Tracheostomy, non-invasive ventilation |

decrease in the risk of hospitalization or death and a virologic efficacy that was similar to that provided by the 2,400 mg dose, the 1,200 mg dose received an EUA (replacing the 2,400 mg dose).

In the Recovery study [10] in hospitalized patients treated with REGEN-COV2 versus standard of care, the results showed that there was only a beneficial effect, reducing mortality at day 28, in those seronegative patients compared to those seropositive.

REGEN-COV2 combination antibody therapy showed efficacy in vitro against several circulating variants of concern and variants of interest, including alpha, beta, delta, and gamma but not against Omicron variant.

**Sotrovimab**. It was identified by screening antibodies from a patient who had been infected during the 2003 SARS-CoV-1 outbreak. The advantage is its ability to also neutralise SARS-CoV-2 because its binding site is a highly conserved pan-sarbecovirus epitope of the SARS-CoV and SARS-CoV-2 spike protein outside the RBD motif. Due to this different and more conserved binding site, its ability to neutralise SARS-CoV-2 implies that mutational escape from different variants is more difficult. The Fc portion of the parent antibody has been modified to extend sotrovimab's half-life to around 49 days. It is given as a single intravenous dose and it has been well tolerated in clinical studies, although occasional serious hypersensitivity reactions have occurred.

Gupta et al in the Comet-Ice study [11] have evaluated the parental form of sotrovimab in a multicenter, double-blind, phase 3 trial, nonhospitalized patients. The study recruited patients with symptomatic COVID-19 (≤5 days after the onset of symptoms) and at least one risk factor for disease progression to receive a single infusion of sotrovimab at a dose of 500 mg or placebo (in a 1:1 ratio). The primary efficacy outcome was hospitalization (for >24 hours) for any cause or death within 29 days after randomization. The population study was comprised by 583 patients (291 in the sotrovimab group and 292 in the placebo group) and most patients have at least 1 risk factor for progression of the disease. The mean age 53 years and 59% of them treatment was initiated within the three days from onset of symptoms. They found that 3 patients (1%) in the sotrovimab group, as compared with 21 patients (7%) in the placebo group, had disease progression leading to hospitalization or death (relative risk reduction, 85%; 97.24% confidence interval, 44 to 96; P = 0.002).

Evidence in hospitalised patients is more limited, and the sotrovimab arm of ACTIV-3 was stopped due to futility after recruiting 344 participants, although no safety concerns were raised. TICO study [12], is a randomized study to compared sotrovimab 500 and a combination of BRII-196 1000 mg plus BRII-198 1,000 mg, in hospitalized patients.

The primary outcome was time to sustained clinical recovery, defined as hospital discharge and remaining at home for 14 consecutive days. Patients included in the study were receiving treatment with Remdesivir and corticosteroids

| Table 2 | Parameters and its punctuation included in the Mass score for prioritize mAbs therapy [15] |
|---|---|

| | Punctuation |
|---|---|
| Age > 65 years | 1 |
| BMI >35 | 1 |
| Diabetes | 2 |
| Renal chronic disease | 3 |
| Cardiovascular chronic disease >55 years | 2 |
| COPD >55 years | 2 |
| Hypertension >55 years | 1 |
| Immunosuppressed patient | 3 |

(around 60%) and the median of days from symptoms onset was 8 days. Patients included different severity (42-45% were receiving O2 <4l/min) and around 58% were seronegative. The results showed no benefit in the arm of sotrovimab. Noteworthy, an important consideration is that the additional antiviral activity from mAbs is not providing incremental benefit in a population treated with remdesivir and corticosteroids.

The appearance of the Omicron has forced to revaluate the activity of the mAbs against this new variant. Touret et al [8] in a preprint showed that sotrovimab maintained activity against Omicron whereas the others exhibited loss of neutralising activity https://covdb.stanford.edu/page/susceptibility-data/).

**Tixagevimab and cilgavimab**. This new long-acting combination mAbs has been authorized for the FDA in USA for pre-exposure prophylaxis proving a new therapeutic approach to avoid the acquisition of the infection [13]. This strategy aims to act in a particularly vulnerable population, such as all those unable to mount an immune response due to pre-existing conditions such as immunocompromised due to transplant or biological treatments. That combination has sought emergency use authorization in USA after demonstration if a phase III trial that it was capable to reduce the risk of COVID-19 symptoms by 77% [14]. It is administrated intramuscularly making the treatment more suitable than intravenous administration.

## CURRENT RECOMMENDATIONS

The current recommendations for indication and prioritization of mAbs depend mainly in three pillars: 1- identification of patient at-risk for developing severe episode 2- timing is crucial to provide treatment within the first 5 days preferably 3. Serological status of patients as it has been reported better favorable outcome in those seronegatives. Several comorbidities and diseases are considered by FDA and EMA (Table 1). Considering prioritization of patients, an score formed with different clinical conditions and age has been proposed (Mass score) (Table 2) to estimate the number needed to treat in re-

lation with number of comorbidities [15]. The requisite is the activity of mAbs against the circulate variants.

The challenge for recommendations is the continuous change of COVID-19 pandemics and the new variants. Nevertheless, National Institutes of Health (NIH) indicates mAbs treatment both in pre-exposure and post-exposure in the out-patient (https://www.covid19treatmentguidelines.nih.gov). The target population are those with high risk of progression or developing severe episode if they get infected. In post-exposure NIH recommends against the use of the anti-SARS-CoV-2 mAbs bamlanivimab plus etesevimab and casirivimab plus imdevimab because they have markedly reduced susceptibility to Omicron, which is currently the dominant SARS-CoV-2 variant. If Omicron variant is suspected or if its prevalence is very high, NIH recommends the use of Sotrovimab.

For hospitalized patients, Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19. Nevertheless, through expanded access programs the products may be available for patients who either have not developed an antibody response to SARS-CoV-2 infection. In Spain, AEMPS https://www.aemps.gob.es/ allows their use in immunosuppressed patients with seronegative patients

## FINAL COMMENTS

In summary, concerning passive immunization mAbs constitute an option for early treatment as they prevent entering viruses into cells mainly directed to patients at higher risk for severe episodes and/or unable to mount and adequate immune response. The main concern is the capacity of new variants to escape from their action [16]. There are several challenges: rapid identification of most vulnerable patients, logistic consideration for endovenous administration and the question of the patient 'serologic status. For prioritization of potential candidates a fast serologic tests is required to determine if patients are seronegative or the amount of Ig G antibodies is low.

There are still several gaps of knowledge mainly in immunosuppressed patients and unanswered questions regarding the evolution of variants of concern, their efficacy, the ideal dosages or mAbs combinations and if there is a threshold point of host Ig G antibodies useful for better personalizing indications.

The near future apparition of oral antiviral will modulate how to prioritize the indications of mAbs versus other alternative oral treatments.

## CONFLICTS OF INTEREST

Rosario Menéndez: Advisory Board and honorarium for educational collaboration in talks and courses for GSK. Rest of authors: none to declare

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