

Short Communication

Endogenous antibody response to SARS-CoV-2 in patients who received monoclonal antibodies against COVID-19: A systematic review

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ABSTRACT

Passive immunization with mAbs has been employed in COVID-19. We performed a systematic review of the literature assessing the endogenous humoral immune response against SARS-CoV-2 in patients treated with mAbs. Administration of mAbs in seronegative patients led to a reduction in both antibody titres and neutralizing activity against the virus.

1. Background

Passive immunization through the administration of monoclonal antibodies (mAbs) directed toward SARS-CoV-2 RBD has represented an innovative approach against COVID-19. Several mAbs have been introduced in the market, employed in primary (tixagevimab/cilgavimab) and secondary prophylaxis (bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, bebtelovimab). Despite the emergence of SARS-CoV-2 variants of concern (VOCs), escaping the immunity provided by these antibodies [1], these drugs are quickly adaptable to pathogens and are going to represent a new element in the therapeutic armoury against several infectious diseases [2].

Some uncertainties remain regarding the impact of mAbs on the endogenous immune response. Indeed, is a well-acknowledged fact that the administration of antigen-specific antibodies can prevent the induction of antibodies against a specific epitope [3]. Moreover, in a mice model, the endogenous antiviral humoral response against RSV was abrogated by the passive immunization with IgG antibodies [4]. Nonetheless, a successful local and systemic immunity can be induced in young infants with circulating maternal Abs who are immunized with live vaccines, suggesting that an efficacious immune response can still be mounted also under the influence of a passively acquired humoral immunity.

It is currently unclear how the endogenous humoral immune response against SARS-CoV-2 is impacted by the administration of mAbs. This is a crucial fact considering the ongoing pandemic with the continuous emergence of VOCs, which is linked to po-

tential repeated exposures to the virus and thus multiple possible reinfections.

2. Materials and methods

We performed a systematic review of the literature employing the string "monoclonal" AND "endogenous" AND "SARS-CoV-2" including studies published between 01/06/2020 and 01/06/2022. Overall, we identified 68 articles, but only three assessing the endogenous humoral immune response against SARS-CoV-2 in patients treated with mAbs (Supplementary Fig. 1). Only two of them underwent peer review [5,6], whereas one is a preprint from the platform medRxiv [7]. Two authors evaluated independently the selected articles, extracting the data relevant to the study objective.

3. Results

Three mAbs/combinations of mAbs were administered, bamlanivimab at different dosages, bamlanivimab + etesevimab or bamlanivimab + etesevimab and casirivimab + imdevimab. Overall, 448 patients received a mAbs infusion whereas 248 subjects were included as control. The endogenous humoral immune response was evaluated heterogeneously across the studies, in terms of antibody titres (Full-length spike with D614G, spike-RBD, spike-RBD E484Q, spike-NTD (N-terminal domain), NCP (nucleocapsid), anti-S IgM, anti-N IgG) and neutralization activity (E484Q, E484K, B.1.351, ACE2 binding inhibition potency, pseudovirus neutralization potency).

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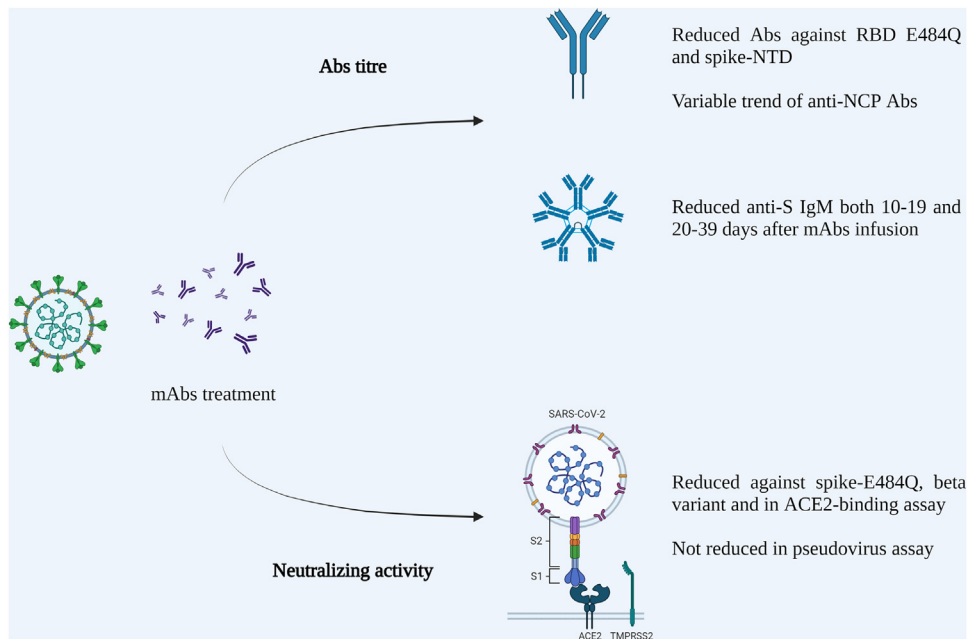


Fig. 1. The impact of mAbs administration on the endogenous immune response.

In the study of Zhang et al. [6], when compared to placebo recipients, the antibody titres against spike-E484K, spike NTD and NCP and against spike NTD and NCP were reduced among patients treated with bamlanivimab and bamlanivimab + etesevimab, respectively. Similarly, Kim et al. [5] identified a reduction of anti-S IgM among individuals treated with bamlanivimab and casirivimab + imdevimab compared to the untreated group, which persisted up to 39 days after mAbs infusion. Anti-N IgG level were less significantly impacted with significant reductions of 50% only in the casirivimab + imdevimab treated group. Interestingly, in a subgroup of patients that was subsequently identified as seropositive for SARS-CoV-2 at time of mAbs infusion, treatment did not significantly reduce the endogenous IgM anti-S or IgG anti-N humoral immune response. Finally, Benschop et al. [7], showed a reduction in spike-RBD-E484Q and spike-NTD titre after vaccination among patients who previously received bamlanivimab or placebo as primary prevention.

Neutralizing activity was assessed in two articles. In the first one [6], the bamlanivimab cohort displayed a reduced neutralizing activity against spike-E484Q and beta variant (E484K, K417N) compared to placebo. Instead, the bamlanivimab + etesevimab cohort showed an increased neutralizing activity against E484Q but a reduced sera neutralization activity against the beta variant. In the second one [7], treatment with bamlanivimab resulted in a lower ability of the endogenous antibody response to inhibit ACE2 binding compared to placebo. Instead, they did not observe a difference in pseudovirus neutralization potency against spike-E484Q for participants who received either placebo or bamlanivimab (Table 1).

4. Discussion

Despite the continuous emergence of new SARS-CoV-2 VOCs able to overcome the activity of mAbs, these treatments represent an innovative strategy to prevent the evolution of the diseases toward the more severe manifestations of COVID-19 and they will probably be applied in several other infectious diseases soon. Here we summarize the preliminary evidence, highlighting how the administration of mAbs against SARS-CoV-2 in COVID-19 seronegative patients led to a reduction in both antibody titres and neutralizing activity against the virus. This reduction is slight, and it remains to be understood the clinical significance, if any. Of note, mAbs have this impact only in patients without antibodies

against SARS-CoV-2 at time of treatment administration. Fig. 1 provide an overview of the impact of mAbs on the endogenous humoral immune response.

To the best of our knowledge, our work is the first one reviewing the impact of mAbs on the humoral immune response against SARS-CoV-2. As stated in the introduction, a previous study performed in mice model showed how passively acquired RSV Abs suppress both systemic and local Ab responses to primary infection with live attenuated RSV vaccine candidates. It must be noted that this did not affect the priming for a secondary Abs response following challenge [4]. Instead, in mice infected with the FrCas^E murine retrovirus, those rapidly subjected to short immunotherapy with neutralizing mAbs survive and mount a long-lasting protective antiviral immunity compared to those untreated who died. In this case, the administered mAbs exerted their effects both via antibody-dependent cell cytotoxicity mechanism and forming immune complexes with infected cells that enhance antiviral CTL responses through FcγR-mediated binding to dendritic cells [8].

Our study has some obvious limitations. First, only few articles have addressed this issue among COVID-19 patients, therefore conclusions are elaborated on a limited amount of experimental evidence. Second, the included work assessed the impact of the first mAbs introduced in the clinical practice and now obsolete due to the emergence of SARS-CoV-2 VOCs escaping their activity and the neutralizing assays employed did not involve more recent VOCs such as gamma and omicron. Third, no data are available on the T cell response, probably a key component in the protection against repeated exposure to the virus [9]. Finally, all the studies provided immunological experimental parameters value, but lack clinical correlates.

Overall, we have highlighted how early treatment of COVID-19 with mAbs led to a slight reduction in antibody titres and neutralizing activity, but the clinical relevance of this reduction is unknown and probably absent. Nonetheless, it is important to acknowledge the impact exerted by these treatments on the endogenous humoral response, considering that mAbs will be employed widely against infectious diseases shortly and especially in immunocompromised patients with an already dysfunctional immune response. It is possible to speculate that this reduction in the humoral immune response is linked to the rapid decrease of viral, and thus antigenic, load obtained with the administration of mAbs. Another option is antigen-specific blockade, with antibodies “hiding” a specific epitope without affecting the response to other antigens. This

Table 1

A global overview of the included studies results.

Study	mAbs administered (number of patients)	Days since enrolment/mAbs administration and samples collection	Humoral responses assessed	Results
Zhang, <i>Front Immunol.</i> 2021	<ul style="list-style-type: none"> – Bamlanivimab 700 mg (99) – Bamlanivimab 2800 mg (104) – Bamlanivimab 7000 mg (97) – Bamlanivimab 2800 mg + etesevimab 2800 mg (108) – Placebo (152) 	<ul style="list-style-type: none"> – 3 – 15 – 29 – 60 – 85 	Ab titres: <ul style="list-style-type: none"> – Full-length Spike (with D614G) – Spike-RBD – Spike-RBD E484Q – Spike-NTD – NCP Neutralization assays: <ul style="list-style-type: none"> – E484Q – E484K – B.1.351 	<ul style="list-style-type: none"> – RBD E484Q, Spike-NTD and NCP Ab titres 1.4 to 4.1-fold lower at day 15–85 in mAbs recipients compared with placebo – Slightly reduced neutralizing activity of day 29 sera from bamlanivimab monotherapy cohorts against both spike-E484Q (factor 3.1, $p = 0.001$) and beta variant (factor 2.9, $p = 0.002$) compared to placebo
Kim, <i>Clinical Immunol.</i> 2022	<ul style="list-style-type: none"> – Bamlanivimab 700 mg (24) – Casirivimab 1200 mg + imdevimab 1200 mg (27) – Bamlanivimab 700 mg + etesevimab 1400 mg (13) – Untreated (34) 	<ul style="list-style-type: none"> – 0–9 (Acute seronegative) – 10–19 (Seroconversion) – 20–39 (Maximum antibody index) 	Ab titres: <ul style="list-style-type: none"> – Anti-S IgM – Anti-N IgG 	<ul style="list-style-type: none"> – 10–19 days after mAbs infusion anti-S IgM levels were reduced by >90% in bamlanivimab and casirivimab + imdevimab treated subjects compared to the untreated group, anti-N IgG levels trended lower but did not reach statistical significance – 20–39 days after mAbs infusion anti-S IgM levels remained reduced by 85–90% in all mAbs treated groups. Anti-N IgG levels were affected to a lesser degree, with significant reductions of 50% only in the casirivimab + imdevimab treated group – Treatment did not significantly reduce the endogenous IgM anti-S or IgG anti-N humoral immune response among baseline seropositive patients ($n = 11$).[#]
Benschop, <i>medRxiv.</i> 2021*	<ul style="list-style-type: none"> – Bamlanivimab 4200 mg (73) – Placebo (62) 	<ul style="list-style-type: none"> – ≤ 64 – 64–85 – >85 	Ab titres: <ul style="list-style-type: none"> – Spike-RBD E484Q – Spike-NTD Neutralization assays: <ul style="list-style-type: none"> – ACE2 binding inhibition potency – Pseudovirus neutralization potency 	<ul style="list-style-type: none"> – Compared with placebo, treatment with bamlanivimab resulted in a 1.8-fold ($p = 0.001$) and 2.0-fold ($p < 0.001$) lower titre against spike-RBD-E484Q and spike-NTD, respectively – Receipt of bamlanivimab resulted in a 4.1-fold ($p < 0.001$) lowering in ability of the endogenous antibody response to inhibit ACE2 binding – There was no statistically significant difference in pseudovirus neutralization potency against Spike-E484Q for participants who received either placebo or bamlanivimab ($p = 0.078$)

mAbs: monoclonal antibodies; RBD receptor binding domain; NTD: N-terminal domain; NCP: nucleocapsid protein.

[#] A subgroup of 11 patients was identified at post-hoc analysis as having positive serology for SARS-CoV-2 at the time of mAbs infusion.

* Subsequently fully vaccinated with two doses of either SpikeVax (Moderna) or Comirnaty (BioNTech/Pfizer) COVID-19 mRNA vaccines.

hypothesis seems less appealing considering how Benschop et al. showed a reduction of Ab-titres (spike-RBD-E484Q, NTD) not specifically bound by the mAb administered (bamlanivimab).

5. Conclusions

Based on the results of our work, no change to the current employment of mAbs is recommended. Future research should be directed at understanding the impact of early mAbs administration on T cell response and at identifying any clinical correlates, to assess the meaningfulness and relevance of the alterations described in our review.

Supplementary Fig. 1 Prisma flowchart of the study.

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Ethical approval

Not required.

Declaration of Competing Interest

AL Gilead Sciences Inc. AB Quiagen, Pfizer, Nordic Pharma, ViiV, SOBI, Gilead Sciences Inc. All the other authors have nothing to declare.

CRediT authorship contribution statement

Andrea Lombardi: Supervision, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Cecilia Azzarà:** Supervision, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Giulia Renisi:** Supervision, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Giulia Viero:** Supervision, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Andrea Gori:** Writing – review & editing. **Alessandra Bandera:** Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.clicom.2022.08.003](https://doi.org/10.1016/j.clicom.2022.08.003).

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