Indication criteria for monoclonal antibody treatment for COVID-19 in the era of vaccination: is an update needed?

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ABSTRACT

This study describes a cohort of 223 patients who received anti-S protein monoclonal antibody (mAb) treatment for COVID-19 after having met the indication criteria set by the national guidelines in the Czech Republic at the time. The authors compare the vaccinated and unvaccinated subpopulations of this cohort. The results show that most of the patients (73.5%) already had significant circulating levels of anti-S antibodies detectable at the time of treatment. The authors confirm a positive correlation between number of vaccine doses and S-protein antibody levels. The data show, that vaccinated patients are overall less likely to be hospitalized than unvaccinated ones. The authors recommend a change in the national guidelines for mAb treatment in the Czech Republic.

KEYWORDS

COVID-19 – anti-SARS-CoV-2 monoclonal antibodies – COVID-19 vaccination – anti-S protein antibodies

SOUHRN

Cimrman Š., Pazderková J., Dvořáková L., Dlouhý P., Hašková K.: Nový pohled na indikační kritéria pro podání monoklonálních protilátek proti covid-19 v éře očkování

Tato studie popisuje kohortu 223 pacientů, kterým byla podána léčba monoklonálními protilátkami proti S proteinu SARS-CoV-2 (mAb) na základě stávajících indikačních kritérií v České republice a porovnává jejich očkovanou a neočkovanou subpopulaci. Dokládá, že většina pacientů (73,5 %) v této kohortě měla již v době podání léčby vysoké hladiny neutralizačních anti-S protilátek. Prokazuje pozitivní závislost mezi počtem dávek očkování proti covid-19 a hladinou cirkulujících anti-S protilátek a dokládá, že očkovaní pacienti v této populaci jsou méně často hospitalizování pro covid-19, než neočkovaní. Na základě těchto výsledků autoři navrhují změny indikačních kritérií pro podání mAb v České republice.

KLÍČOVÁ SLOVA

covid-19 – monoklonální protilátky anti-SARS-CoV-2 – očkování proti covid-19 – protilátky proti proteinu S

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BACKGROUND

Monoclonal anti-S protein antibody (mAb) infusions have been an available treatment option for patients with COVID-19 in the Czech Republic since May 2021. This cohort study presents an overview of 223 patients who received this treatment, including vaccination status and anti-S protein antibody levels at the time of the infusion. We compared patient subpopulations based on their vaccination status and traced their clinical outcome after the mAb application.

Although the widespread dominance of the Omicron variant of COVID-19 caused a shift towards other treatment options [1], it is expected that new and emerging mAbs that retain their efficacy against COVID-19 variants (Sotrovimab, Tixagevimab plus Cilgavimab, etc.) will be available in the Czech Republic soon. Our goal is to recommend the distribution of these scarce medical resources to patients that will benefit from them the most.

METHODS

In this prospective study, we collected and processed data from 223 patients who received mAb treatment in our outpatient clinic between September 2021 and January 2022. This treatment was only recommended to specific groups of patients considered to be at a high risk of disease progression. The indication criteria were

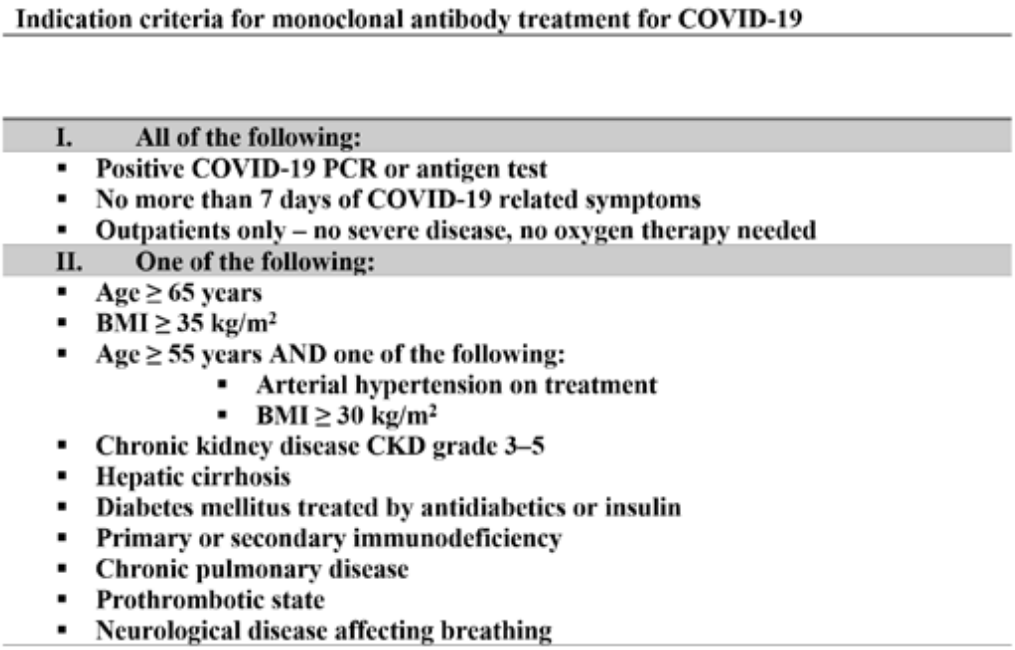

Figure 1. Indication criteria for mAb treatment – published November 22, 2021 [2]
Full list was abbreviated for the sake of brevity, contains main criteria only.

defined by the national guidelines at the time [2]. Before application, a patient's venous blood sample was collected and informed consent was given.

We calculated the 95% confidence intervals for the ratio of seropositive patients. Fisher exact test has been used to evaluate the dependence of COVID-19 vaccination and hospitalization for COVID-19 related health issues. 5% significance level has been chosen, 95% confidence intervals for the odds ratio have been calculated. Spearman correlation coefficient has been calculated to evaluate the dependence of anti-S protein antibody levels and number of vaccination doses.

FINDINGS

Out of the 223 patients in our cohort, 164 (73.5%) already had detectable anti-S protein antibodies at the time of the infusion (95% CI = 67.0, 79.0). 119 of these patients had anti-S protein antibody levels equivalent to more than 250 BAU/ml.

We used the following mAb regimens: Bamlanivimab (n = 30), Casirivimab/imdevimab (n = 159), Regdanvimab (n = 34). We saw patients qualify for mAb treatment under following criteria: age 65 or higher (n = 119), body mass index (BMI) 35 or higher (n = 34), age 55 or higher + arterial hypertension (n = 22), immunodeficiency (n = 18), diabetes mellitus treated by antidiabetics or insulin (n = 17), prothrombic state (n = 5), age 55 or higher + BMI 30 or higher (n = 4), chronic pulmonary disease (n = 4).

166 patients in our cohort were vaccinated, 54 patients were not. In the case of 3 patients, the vaccination status was not determined. The circulating titer of anti-S protein antibodies was significant in all but 8 (4%) vaccinated patients in our sample and was higher in patients who received multiple doses of the COVID-19 vaccines ($p < 0.0001$). In contrast, only 5 (9.2%) unvaccinated patients had any anti-S protein antibodies detectable at the time. Median titer of anti-S antibodies was 123.76 BAU/mL in patients who received 1 vaccination dose (n = 17), 218.71 BAU/ml in patients who received 2 doses (n = 118) and 241.94 BAU/mL in patients who received 2 doses and a booster (n = 31).

Only 4 (2.4%) of the vaccinated patients in our cohort had to be hospitalized for COVID-19 following the mAb infusion. In comparison, 6 (11%) of the unvaccinated patients had to be hospitalized. The vaccinated patients were therefore less likely to be hospitalized for COVID-19 ($p = 0.1573$; CI 95% = 0.004, 0.88).

CONCLUSION

Based on the indication criteria at the time, mAb infusions had been administered in most cases to patients who already had preexisting significant and likely protective levels of circulating anti-S protein antibodies.

Based on our findings, we suggest most of the patients that are considered at high-risk of disease progression as we currently identify them already have more than sufficient levels of neutralizing anti-S protein antibodies.

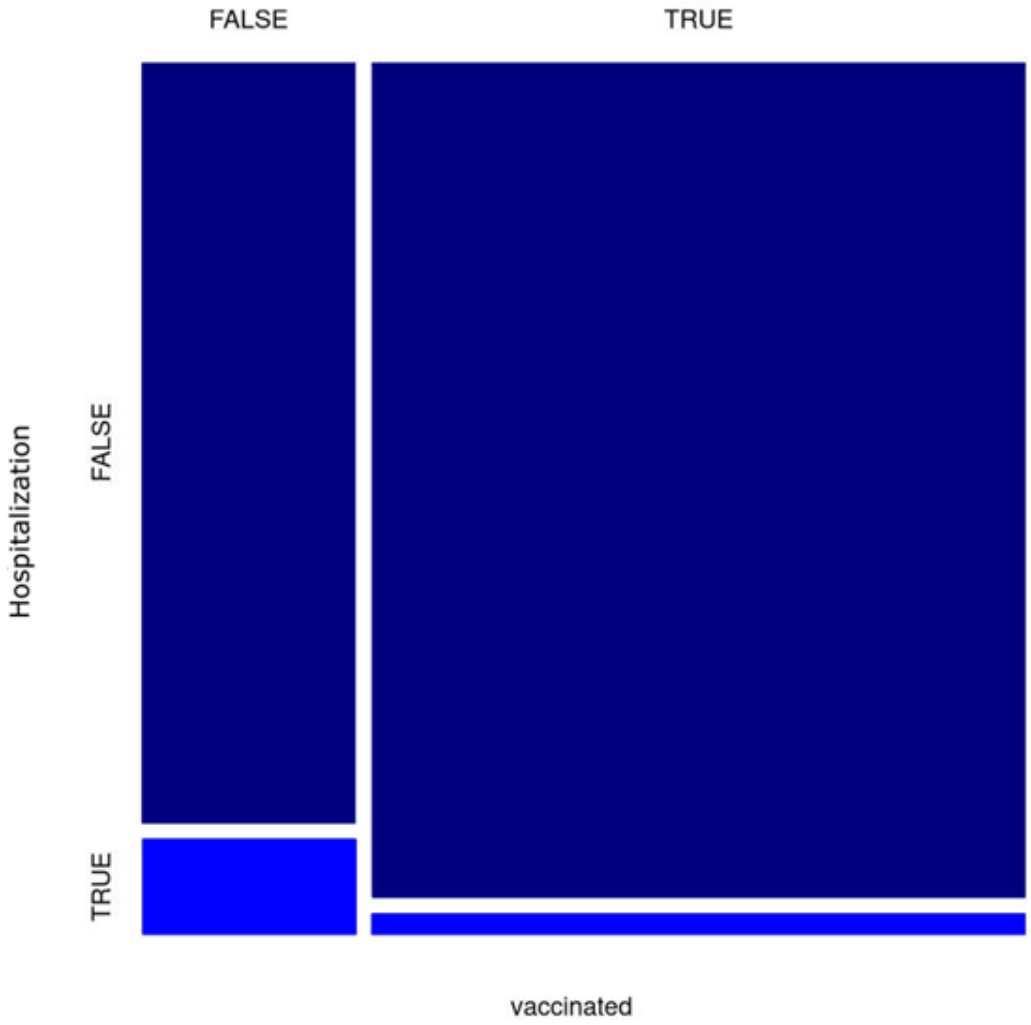

Figure 2. Mosaic plot for comparison of patient subpopulations based on vaccination status and need for hospitalization for COVID-19
Top left: patients who were not vaccinated and were not hospitalized (n = 48). Top right: patients who were vaccinated and were not hospitalized (n = 162). Bottom left: patients who were not vaccinated and were hospitalized (n = 6). Bottom right: patients who were vaccinated and were hospitalized (n = 4).

DISCUSSION

In patients with significant anti-S protein antibody levels, the application of mAb could be considered wasteful, as it is likely not to have a significant impact on their clinical outcome [3]. Evidence suggests that people who become seropositive following infection or primary vaccination will produce antibodies with increased potency and breadth than those we are able to produce artificially [4].

In most patients, the presence of preexisting endogenous neutralizing anti-S antibodies can be attributed to prior vaccination – the complex immunogenic potential of COVID-19 vaccines has been extensively documented by other authors [5]. Evidence suggests, that anti-S protein antibodies can be used as a protective corelate for COVID-19 vaccines, even though the exact range of neutralizing antibody titer, that could be considered protective, is currently not yet established [6].

We therefore recommend the following changes in the national indication guidelines:

• Given the increased availability of point-of-care methods [7], future applications of mAb (including the upcoming Sotrovimab) should be reserved for patients with a confirmed lack of circulating anti-S protein antibodies. We suggest prioritization of other treatment modalities for seropositive patients.

• In settings, where point-of-care methods to detect anti-S protein antibody levels are unavailable, unvaccinated patients should be prioritized.

This recommendation is in line with conclusions of larger clinical studies (RECOVERY trial, etc.) and NIH guidelines [8, 9].

Unfortunately, most available studies concerning the efficacy of mAb treatment regimens are based on unvaccinated populations. Despite that, new studies that support our suggestion to reserve mAb treatment for anti-S antibody-negative patients are beginning to appear [10].

Limitations

The values of neutralizing antibody levels described in relation to vaccination dosage may be skewed due to our laboratory's upper detection limit value being 250 BAU/mL. The list of indication criteria, under which patients qualified for mAb treatment, may be imprecise, since in case of multiple simultaneous risk factors occurring in the same patient, only one was selected at the discretion of the physician.

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