THE CUTTING EDGE: RESEARCH UPDATE



Antibody therapies for treatment of non-severe COVID-19

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Background

As the global COVID-19 pandemic reaches its 2nd year, over 270 million cases and 5.3 million deaths have occurred globally. Nearly, 3000 clinical trials have been approved for therapy evaluation, of which approximately 350 evaluate the efficacy of cellular or monoclonal antibody (mAB)-based therapies.

The purpose of this appraisal is to evaluate the efficacy of mABs for non-severe COVID-19. mABs are recombinant proteins that can bind to structures with a neutralizing effect, limiting the virus's ability to act and reproduce within human cells. mABs have shown more promising effects in individuals with non-severe COVID-19, while there is a lack of consensus on efficacy for severe cases. Understanding the relative efficacy of mABs in non-severe disease may allow hospitals to treat patients proactively, ultimately preventing hospital admissions and disease progression.

The WHO's Living Systematic Review and Network Meta-Analysis for antibody and cellular-based therapies [1] was developed to summarize research for this purpose. Timely appraisal of the current evidence is paramount to developing treatment protocols and ensuring that resources are managed appropriately, providing the greatest chance at reducing morbidity and mortality from COVID-19 on a global scale.

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Abstract of the study

This is the latest iteration of a living systematic review, published Sept 23rd, 2021, meaning that updates are integrated with each iteration of literature searches. Daily searches are made by the WHO, including over 25 "bibliographic and grey literature sources" found in the US Center for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database. Study selection included preprints—primary research articles that have been released to the public before peer review. Preprints were tracked until publication, and changes were made to the guidelines if discrepancies existed between the preprint and peer-reviewed versions.

Trial characteristics, patient demographics, donor characteristics and clinically important outcomes were recorded for each selected article. Outcomes for patients with severe and non-severe disease were studied separately. This severity was determined by the WHO severity scale: non-severe disease mandated that patients have O_2 sats > 90% on room air, no signs of pneumonia, and no other clinical signs or symptoms of respiratory distress.

Outcomes of interest were decided upon by a team of clinical experts, and included: mortality, mechanical ventilation, adverse events leading to discontinuation within 28 days, viral clearance, TRALI, TACO, infusion reactions, admission to hospital, hospital stay time, ICU length of stay, time to symptom resolution, time to viral clearance. Importantly, side effects of mABs not addressed in these outcomes may include anaphylaxis and sequelae of allergic reactions. mAB infusion may also induce bleeding, soreness, or infection at the site of administration.

Fourteen different antibody or cellular treatments were evaluated for the treatment of COVID-19. This review focuses only on the evaluation of 12 studies of 5 monoclonal antibody therapies: bamlanivimab (LY-CoV555; 4 trials), casirivimab-imdevimab (REGEN-COV; 4 trials), bamlanivimab-etesevimab (2 trials), sotrovimab (1 trial), and CT-P59 monoclonal antibody (1 trial). 54.5% of these were preprints. Once preprints were published, there were

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no statistically significant differences in either outcomes or patient characteristics when comparing the preprint and peer-reviewed publication.

There was a lower risk of hospital admission in patients with non-severe COVID-19 when treated with mAB therapy compared to standard care alone: casirivimab-imdevimab odds ratio (OR) 0.29 (95% CI 0.17–0.47); bamlanivimab OR 0.24 (95% CI 0.06–0.86), bamlanivimab-etesevimab OR 0.31 (95% CI 0.11–0.81), sotrovimab OR 0.17 (95% CI 0.04–0.57) and CT-P59 OR 0.48 (95% CI 0.14–1.60). Only casirivimab-imdevimab was shown to have moderate certainty evidence for this outcome; others were rated lower due to small numbers of events. With an assumed hospitalization rate for COVID-19 of 2.1% [2], the number needed to treat (NNT) for casirivimab-imdevimab to reduce the risk of hospital admission was 67 (Calculated separate from publication; OR = 0.29, PEER = 0.021).

Only casirivimab-imdevimab (ratio of means 0.72; 95% CI 0.58–0.92, moderate certainty) was shown to reduce duration of symptoms of non-severe COVID-19. Bamlanivimab (ratio of means 0.92; 95% CI 0.64–1.32, low certainty), bamlanivimab-etesevimab (ratio of means 0.89; 95% CI 0.68–1.16, moderate certainty), and CT-P59 (ratio of means 0.66; 95% CI 0.42–1.05, moderate certainty) did not reduce symptom duration.

None of the mABs studied showed a difference in mortality for non-severe COVID-19: casirivimab-imdevimab OR 0.58 (95% CI 0.26–1.22), bamlanivimab OR 0.46 (95% CI 0.01–27.79), bamlanivimab-etesevimab OR 0.05 (95%

Table 1 Appraisal summary, based off the AMSTAR2 Tool [3]

CI 0.00–1.01), sotrovimab OR 0.33 (95% CI 0.01–10.16), CT-P59 OR 0.51 (95% CI 0.01–30.40). Non-severe disease has an inherently low risk of mortality, which may have impacted these outcomes.

Strengths of the study

- This study was appraised using the AMSTAR2 tool, a validated assessment method for systematic reviews and meta-analyses [3]. An abbreviated version has been summarized here (See Table 1). The study scored optimally in all but two categories, demonstrating well-defined methods and a comprehensive search strategy.
- The data on COVID-19 treatments are quickly accessible through this open access publication, and has continued to be updated with relevant updates on novel therapies.
- The search strategy incorporated multiple international databases and publications, strengthening the external validity of the findings.

| AMSTAR criterion | Fulfilled crite- ria? (Yes/No) | Comments |
|--|-----------------------------------|---|
| PICO Question Identified? | Yes | |
| Methods established prior to review? | Yes | |
| Use of comprehensive literature search strategy? | Yes | |
| Study selection in duplicate? | Yes | |
| Data extraction in duplicate? | Yes | |
| Describe included studies in adequate detail? | Yes | Described population, intervention, comparison, study's set- ting, and timeframe |
| Explanation of selection of study designs? | No | NRSI's not included |
| Excluded studies justified? | Yes | Non-RCT's were removed from the review |
| Risk of bias assessed with a validated technique, for both systematic reviews and meta-analyses? | Yes | |
| Appropriate method of statistical combination of results? | Yes | |
| Report on sources of funding for included studies? | No | |
| Risk of bias addressed when interpreting results? | Yes | |
| Discussion of small study bias on review results? | Yes | Studies with low numbers of outcome events were rated as hav- ing lower certainty evidence |
| Potential sources of conflict discussed? | Yes | Discusses both competing interests as well as source of funding |

AMSTAR criterion, summarized in table format with results from the completed appraisal. Comments reflect reasons for or against the fulfillment of criteria

Weaknesses of the study

 This review excluded studies that evaluated efficacy of COVID-19 prophylaxis or vaccination. As a result, the patient population addressed in this study is unvaccinated and mAB efficacy may be different in vaccinated groups.

Sponsorship

• Sponsorship was provided for this study by the Canadian Institutes of Health Research.

Question marks

- This systematic review does not include confirmed Delta or Omicron variant cases. Emerging research on the Omicron variant has demonstrated resistance to many mABs discussed in this article. Sotrovimab is the only mAB to demonstrate a significant decrease in all-cause hospitalization in populations infected with the Omicron variant [4]. We wonder if mABs will prove effective in treating this subset of non-severe COVID-19 infections.
- This systematic review does not address timing of administration as a variable for mAB efficacy. We wonder if earlier mAB administration leads to improved outcomes for patients with non-severe COVID-19?
- Preprints have become an important component of available research for COVID-19 treatments [5]. We wonder how their inclusion could impact the body of knowledge on this topic, given the inherent lack of a peer-review process?

Clinical bottom line

Monoclonal antibody therapy may reduce hospitalization and symptom duration in non-severe COVID-19.The lack of evidence for mAB therapy against emerging variants of concern, including the Delta and Omicron variants, warrants urgent further research.

Author contributions All authors contributed to the manuscript conception. KG and NT performed the appraisal of the article to be reviewed. The first draft of the manuscript was prepared by KG, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflicts of interest The authors have no conflicts of interest to disclose.

Statement of human and animal rights The authors have not performed any studies with human participants or animals for the purposes of this article.

Informed consent For this type of study formal consent is not required.

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