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Neutralizing Antibodies for Outpatient Treatment of COVID-19

Introduction

Neutralizing monoclonal antibodies are a promising therapy for outpatient treatment of mild to moderate COVID-19. The goal of outpatient therapy is to prevent respiratory distress and hospitalization in those at risk for clinical deterioration. Recently, the FDA granted Emergency Use Authorization (EUA) to bamlanivimab (LY-CoV555) with or without etesevimab[1], and the combination casirivimab/imdevimab (REGN-CoV2)[2] for this indication. This newsletter will review the currently published data for these therapies, discuss current NIH and IDSA guidelines[3,4] for their use, and highlight logistical concerns regarding implementation.

In the Literature

In January 2021, Chen, Gottlieb, and colleagues simultaneously published interim and final results from the BLAZE-1 trial in *NEJM* and *JAMA*, respectively.[5,6] This trial investigated the effect of single-dose bamlanivimab +/- etesevimab on viral replication of COVID-19. These drugs are neutralizing antibodies targeting the SARS-CoV-2 spike protein. Eligible participants were 18 years and older, with mild or moderate symptoms (defined by FDA guidance) and a positive SARS-CoV-2 test obtained in the previous 72 hours. Ultimately, 577 subjects were randomized in 1:1:1:1:1 fashion to receive either IV bamlanivimab monotherapy at 700 mg, 2800 mg, 7000 mg; 2800 mg IV bamlanivimab combined with 2800 mg IV etesevimab; or IV normal saline infusion. The median duration from time of symptom onset to infusion was 4 days. The primary outcome assessed was change in viral load from baseline at day 11. Results were mixed—bamlanivimab monotherapy did not significantly reduce viral load compared with placebo, while the combination of bamlanivimab and etesevimab did appear to improve SARS-CoV-2 viral load burden at follow up. However, the frequency of COVID-19 hospitalization or emergency department (ED) visit differed between the bamlanivimab and placebo arms. Roughly 1.5% (6/421) of patients receiving bamlanivimab (or bamlanivimab and etesevimab) versus approximately 6% (9/156) of individuals receiving placebo required hospitalization or ED visit at study day 29. Although the study was not designed to evaluate clinical outcomes, this finding suggests bamlanivimab, with or without etesevimab, may mitigate COVID-19-related emergency visits and hospitalizations. No serious adverse events were reported with bamlanivimab or etesevimab infusion.

Concurrently, Regeneron sponsored a trial of combination therapy with casirivimab and imdevimab (REGN-CoV2) and published interim results in January 2021.[7] Like bamlanivimab and etesevimab, these drugs are also neutralizing antibodies targeting the SARS-CoV-2 spike protein. Eligibility criteria closely mirrored the BLAZE-1 trial. Two hundred and seventy-five patients were randomized to receive either placebo, 2.4 grams of REGN-CoV2, or 8.0 grams of REGN-CoV2 in 1:1:1 fashion. The median time from symptom onset to infusion was 3 days. Again, the primary study outcome was virologic, the time-weighted average reduction in viral load over 7 days which was statistically significant. A secondary outcome evaluated the number of medically attended visits through the 29-day study period. While not statistically significant, 6% (6/93) of subjects in the placebo group required medical attention, compared with only 3% (6/182) of individuals receiving REGN-CoV2. Six serious adverse events occurred with REGN-CoV2 therapy, although none were directly attributed to the drug cocktail.

On the basis of these data, the FDA granted EUAs to bamlanivimab monotherapy, and bamlanivimab / etesevimab and casirivimab / imdevimab combination therapy. The EUAs encompass individuals 12 years or older, with mild to moderate COVID-19, in the

outpatient setting, who are at high risk of progressing to severe COVID-19 disease. **It is essential to note these drugs are not approved under any circumstances for inpatient use.**

FDA High Risk Criteria for Severe COVID-19
Body mass index (BMI) ≥ 35
History of chronic kidney disease
History of diabetes
History of immunosuppressive disease
Age ≥ 65 years
Age ≥ 55 years AND • History of cardiovascular disease, OR • History of hypertension, OR • History of chronic respiratory disease

In the Guidelines

As of February 11th, neither the NIH nor IDSA COVID-19 treatment guidelines recommend the routine outpatient use of bamlanivimab or casirivimab / imdevimab for mild to moderate disease, citing insufficient data alone.[3,4] However, NIH just released a statement (as of 2/23/21) recommending, *when available,* the combination of bamlanivimab 700 mg plus etesevimab 1,400 mg for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, defined by the EUA criteria. The BLAZE-1 and REGN-COV2 trials each suggested risk reduction of hospitalization with neutralizing antibody therapy, but overall trial numbers were small, and the clinical significance of this finding remains uncertain. Furthermore, the safety profile for these drugs remains relatively unknown. Anaphylaxis and hypersensitivity have been reported with bamlanivimab, while casirivimab/imdevimab has caused infusion reactions.[1,2] Both trials continue to enroll patients to evaluate additional clinical outcomes in phase 3 studies. As this data becomes available, the NIH and IDSA guidelines are likely to change in the near future.

Regarding the variants of SARS-CoV-2

The SARS-CoV-2 variants that have appeared in other parts of the world and now detected in the US have raised concerns about the extent to which their mutations may allow them to evade these current antibody treatments and vaccines. Regarding the potential to escape from these currently available neutralizing antibodies, a group from Fred Hutchison Cancer Research Center in Seattle, WA created >3,800 fragments with mutations of the specific domain of the SARS-CoV-2 spike protein that is crucial for binding of human cells.[8] They then used standard laboratory techniques to assess how these mutations affected the ability of these currently available antibodies to bind to the virus. They found a few mutations that would affect binding of each individual mAB in the REGN-COV2 cocktail, but only one mutation that would allow the virus to escape both. Similarly, there were mutations discovered that would allow for the virus to escape bamlanivimab. They note that several of these mutations were already present in circulating virus strains.

Specifically, regarding the current notorious variants B.1.351 and B.1.1.7, Columbia University researchers have submitted a paper for peer-review after independently confirming findings from both Regeneron and Ely Lily.[9] The REGN-COV cocktail successfully neutralizes both variants. The B.1.351 does have one mutation that allows escape from one mAB in this cocktail but not both. However, the Ely Lily mAB, bamlanivimab, is inactive against the B.1.351 variant but remains active against the B.1.1.7 strain. We do not have data yet on the etesevimab and its ability to bind these variants.

In the Outpatient setting

With current clinical equipoise for neutralizing antibodies in the outpatient treatment of COVID-19, a large pool of potential recipients, and potentially scarce supply, antimicrobial stewardship programs (ASPs) are well positioned to assist health systems regarding use of these medications.[10]

Understandably, this can present a tremendous burden to stewardship teams already stretched with the burden of managing inpatient COVID treatments and assisting with the COVID vaccine rollout. Therefor,

several strategies including pre-built or computerized order sets and check-list based approval criteria that may help ensure therapy is targeted to appropriate patients while conserving ASP resources for other ongoing initiatives.

There is no one correct solution for managing usage of neutralizing antibodies for COVID-19 disease. Health systems will have to evaluate their outpatient framework and determine the best fit for addressing these new therapies.

One last note, in the scenario when the patient is sick with COVID who has already been vaccinated, CDC recommends that their treatment decisions should not be affected by their vaccination status, including the use of monoclonal antibodies.

Conclusion

In the future, additional data from phase 3 studies of bamlanivimab, etesevimab, casirivimab, and imdevimab should shed further light on their clinical utility (or lack thereof) for mild and moderate COVID-19 disease. Until that time, decisions to administer these drugs should be made on a case by case basis. However, programs should develop contingency plan for broader utilization of these drugs. For aid in implementing such plans, please reach out to your DASON liaison, who will be happy to assist.

Key Points

- **Bamlanivimab, bamlanivimab/etesevimab, and casirivimab/imdevimab are promising therapies for outpatient treatment of mild and moderate COVID-19 disease.**
- **More data from ongoing phase 3 trials is needed to determine any significant clinical benefit to neutralizing antibody infusion**
- **In the absence of data, current guidelines are ambivalent in recommendations for or against bamlanivimab alone**
- **SARS-CoV-2 variants may reduce the effectiveness of the currently available monoclonal antibody treatments**
- **Currently, treatment should be considered on a case-by-case basis**
- **DASON liaisons are available to assist health systems in troubleshooting usage of neutralizing antibodies.**

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