Update on monoclonal antibody treatments for COVID-19

Eleftherios Mylonakis, M.D., Ph.D., FIDSA, FAAM
Charles C.J. Carpenter Professor of Infectious Disease
Professor of Molecular Microbiology and Immunology,
Chief, Infectious Diseases Division
Assistant Dean for Outpatient Investigations
Director, Center for Outpatient and Longitudinal Medical Research
Director, COBRE Center for Antimicrobial Resistance and Therapeutic Discovery
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Regeneron – Antibody cocktail to SARS-CoV-2 spike protein (REGN10933 and REGN10987)

- REGN-COV2 (REGN10933 and REGN10987) is a cocktail made up of two noncompeting, neutralizing human IgG1 antibodies that target the receptor-binding domain of the SARS-CoV-2 spike protein, thereby preventing viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor.

- REGN10933 and REGN10987 each bind monomeric and dimeric recombinant SARS-CoV-2 RBD with nanomolar and picomolar affinities, respectively, and stabilized, trimerized SARS-CoV-2 S protein with picomolar affinities.


Based on these criteria, selected pairs of highly-potent individual antibodies that simultaneously bind the receptor-binding domain of the spike protein, providing ideal partners for a therapeutic antibody cocktail that aims to decrease the potential for virus escape mutants that might arise.
REGN-COV2 rapidly reduced viral load through Day 7 in seronegative patients (key virologic endpoint)

Analysis (n=799): 57% reduction in the proportion of patients with medically-attended visits for COVID-19 (2.8% combined treatment arms vs 6.5% placebo, p=0.024).

Similar treatment effects were observed in the two dose levels tested (2.4 g low dose; 8.0 g high dose)

Serious adverse events were numerically more frequent with placebo than REGN-COV2 treatment (0.8% high dose, 1.6% low dose; 2.3% placebo).

Infusion reactions: 1.5% high dose; 0% low dose; 0.4% placebo).

Virologic effects were most pronounced in patients who had high viral loads and/or were SARS-CoV-2 sero-antibody negative at baseline.
Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial
https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1

- Randomized, controlled, open-label trial
- Eligible and consenting patients were randomly allocated (1:1) to either usual standard of care alone (usual care group) or usual care plus a single dose of REGEN-COV 8g (casirivimab 4g and imdevimab 4g) by intravenous infusion (REGEN-COV group).
- The primary outcome was 28-day mortality assessed first among patients without detectable antibodies to SARS-CoV-2 at randomisation (seronegative) and then in the overall population.
- 9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone, including 3153 (32%) seronegative patients, 5272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status.
- In the primary efficacy population of seronegative patients, 396 (24%) of 1633 patients allocated to REGEN-COV and 451 (30%) of 1520 patients allocated to usual care died within 28 days (rate ratio 0.80; 95% CI 0.70-0.91; p=0.0010).
- In an analysis involving all randomised patients (regardless of baseline antibody status), 944 (20%) of 4839 patients allocated to REGEN-COV and 1026 (21%) of 4946 patients allocated to usual care died within 28 days (rate ratio 0.94; 95% CI 0.86-1.03; p=0.17).
- The proportional effect of REGEN-COV on mortality differed significantly between seropositive and seronegative patients (p value for heterogeneity = 0.001).
SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

101 Patients were enrolled and assigned to 700 mg of LY-CoV555 monotherapy
107 Patients were enrolled and assigned to 2800 mg of LY-CoV555 monotherapy
101 Patients were enrolled and assigned to 7000 mg of LY-CoV555 monotherapy
143 Patients were enrolled and assigned to placebo

Interim Analysis
Positive SARS-CoV-2 test ≤3 days before infusion
Mild or moderate Covid-19 symptoms
Primary end point: change from baseline to day 11 (+4 days) in SARS-CoV-2 viral load
Secondary end points include safety, symptom severity, hospitalization, and time points for viral clearance

Figure 1. Enrollment and Trial Design.

Figure 2. SARS-CoV-2 Viral Load in All Patients and According to Trial Group on Day 7.
Panel A shows the SARS-CoV-2 viral load (as measured by the cycle threshold on reverse-transcriptase–polymerase-chain-reaction assay) for all the patients who received either LY-CoV555 or placebo and for whom viral-load data were available at the time of the interim analysis. The box plots indicate the patients who were not hospitalized, and the red squares indicate those who were hospitalized. Such hospital contact was found to be associated with a high viral load on day 7. The boxes represent interquartile ranges, with the horizontal line in each box representing the median and the whiskers showing the minimum and maximum values (excluding outliers that were more than 1.5 times the values represented at each end of the box). Panel B shows the cumulative probability that patients in each trial group would have the indicated cycle threshold of viral load on day 7.

Figure 3. Symptom Scores from Day 2 to Day 11.
Shown is the difference in the change from baseline (delta value) in symptom scores between the LY-CoV555 group and the placebo group from day 2 to day 11. The symptom scores ranged from 0 to 24 and included eight domains, each of which was graded on a scale of 0 (no symptoms) to 3 (severe symptoms). The bars represent 95% confidence intervals. Details about the symptom-scoring methods are provided in the Supplementary Appendix.

Table 3. Hospitalization.

<table>
<thead>
<tr>
<th>Key Secondary Outcome</th>
<th>LY-CoV555</th>
<th>Placebo</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night 7</td>
<td>700 mg, 1/101</td>
<td>2800 mg, 2/107</td>
<td>7000 mg, 2/107</td>
</tr>
</tbody>
</table>

* Data for patients who presented to the emergency department are included in this category.
Pause in the Distribution of bamlanivimab/etesevimab

June 25, 2021

The Assistant Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA) within the U.S. Department of Health and Human Services are committed to ensuring timely and transparent communication regarding the COVID-19 monoclonal antibody treatments currently authorized for emergency use in certain patients with COVID-19.

Today, we are informing you that ASPR is immediately pausing all distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing supply of bamlanivimab at a facility for use under EUA (94)) on a national basis until further notice. In addition, FDA recommends that health care providers nationwide use alternative authorized monoclonal antibody therapies, as described below, and not use bamlanivimab and etesevimab administered together at this time.

The Centers for Disease Control and Prevention (CDC) has identified that the combined frequencies of the SARS-CoV-2 P.1/Gamma variant (first identified in Brazil) and the B.1.351/Beta variant (first identified in South Africa) throughout the United States now exceed 11% and are trending upward (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html). Results from in vitro assays that are used to assess the susceptibility of viral variants to particular monoclonal antibodies suggest that bamlanivimab and etesevimab administered together are not active against either the P1 or B.1.351 variants. These assays use "pseudotyped virus-like particles" that help determine likely susceptibility of the live SARS-CoV-2 variant viruses.

REGEN-COV and sotrovimab are alternative monoclonal antibody therapies that are currently authorized for the same use as bamlanivimab and etesevimab administered together. Based on similar in vitro assay data currently available, REGEN-COV and sotrovimab are likely to retain activity against the P1 or B.1.351 variants. All treatment delivery sites can continue ordering REGEN-COV from the authorized distributor by following the existing ordering and reporting procedures. All treatment sites may also find information on the availability and ordering of sotrovimab by visiting GileadSmithKline’s website at www.sotrovimab.com.

Healthcare providers should review the Antiviral Resistance information in Section 15 of the authorized Fact Sheets for each monoclonal antibody therapy available under an EUA for details regarding specific variants and resistance. Healthcare providers should also refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) and information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Monoclonal antibody therapies available under an EUA must be used in accordance with the terms and conditions for the respective authorization, including the authorized labeling. The Letters of Authorization may be accessed at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

ASPR and FDA will continue to work with the CDC and the National Institutes of Health on surveillance of variants that may impact the use of the monoclonal antibody therapies authorized for emergency use. We will provide further updates and consider additional action as new information becomes available.
GlaxoSmithKline – Dual-action monoclonal antibody VIR-7831

- VIR-7831 is a fully human IgG1 kappa (IgG1κ) mAb derived from the parental mAb S309, a potent neutralizing mAb directed against the spike protein of SARS-CoV-2.

- S309 binds to a highly conserved epitope of the SARS-CoV and SARS-CoV-2 spike protein receptor binding domain (RBD) and inhibits SARS-CoV-2 infection in vitro.

FDA issues EUA for sotrovimab, third monoclonal antibody to treat COVID-19

The FDA has issued an emergency use authorization for the monoclonal antibody sotrovimab to treat mild-to-moderate COVID-19 in patients at risk for progressing to severe disease, according to a press release.

The emergency use authorization — now the third for a monoclonal antibody in the treatment of COVID-19 — is specifically for adults and children aged 12 years and older who weigh at least 40 kg, or approximately 88 pounds. It is not intended for patients who are...
Authorized Use and Limitations

Sotrovimab received Emergency Use Authorization by the FDA on May 26, 2021

Authorized Use

- Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- Sotrovimab is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
AstraZeneca – AZD7442 a combination of two mAbs - tixagevimab (AZD8895) and cilgavimab (AZD1061)

- AZD7442 is comprised of 2 mAbs, AZD8895 and AZD1061, which were derived from B cells isolated from convalescent patients.

- AZD8895 and AZD1061 bind the RBD of the SARS-CoV-2 spike protein with nanomolar affinity and are individually able to sterically block virus recognition of the hACE2 receptor as a mechanism of action.

- Target unique, non-overlapping epitopes on the RBD and bind concurrently to provide redundancy in protection in case of viral mutation and escape.

In Vitro Neutralization Activity Against USA-WA1/2020 Strain of SARS-CoV-2

The function of monoclonal antibodies in suppressing cytokine storm during COVID-19 infection (Created by Tahmasebi et al.).
Thank You
Grazie
Takk
Thank You
DANKE
Merci
Thanks
Thank You
Gracias
Thank You
Obrigado

el.mylonakis@gmail.com