Therapies for COVID-19

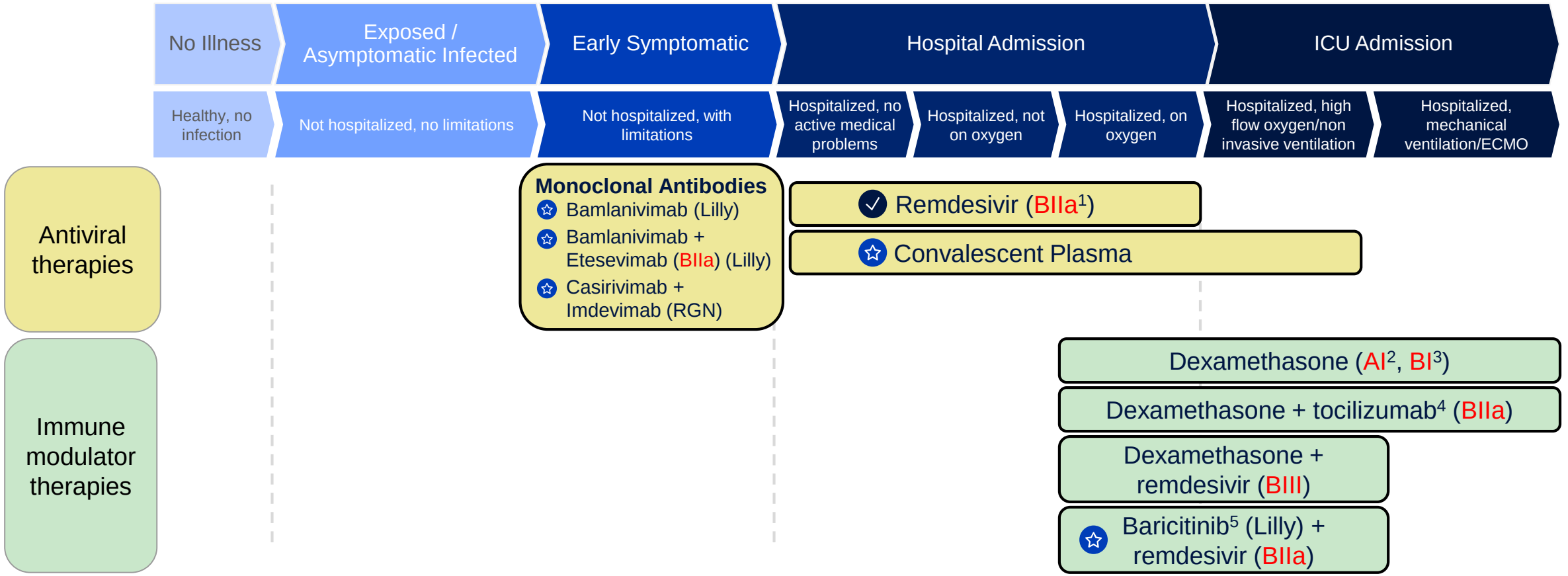
Meredith K. Chuk, M.D.
Lead, COVID-19 Therapeutics Team
HHS/ASPR COVID-19 Outpatient Therapeutics Mini-Series

MARCH 24, 2021

Agenda

1. Summary of COVID-19 Therapeutics
2. Current monoclonal antibodies available under EUA
3. Impact of variants
4. COVID-19 therapies in development

Summary of available COVID-19 Therapeutics



Note: Ratings represent NIH treatment guideline recommendations - Rating of Recs: A = strong; B = moderate; C = optional; **Rating of Evidence:** I = one or more randomized trials without major limitations; IIa = other randomized trials or subgroup analyses of randomized trials; IIb = nonrandomized trials or observational cohort studies; III = expert opinion

Key: ✓ FDA approved ☆ EUA issued

1. BIIa rating only applicable for patients who require minimal supplemental oxygen; insufficient data for use in patients without oxygen requirement; 2. A1 rating for patients requiring invasive mechanical ventilation or ECMO; 3. BI rating for hospitalized requiring supplemental oxygen; 4. For hospitalized patients requiring conventional oxygen supplementation, use rem, dex+rem or dex; 5. In the rare circumstance corticosteroids cannot be used, baricitinib + remdesivir can be used Source: NIH COVID-19 Treatment Guidelines, "Therapeutic Management of Adults with COVID-19"; UpToDate.com, "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults"

Emergency Use Authorizations (EUAs) for Monoclonal Antibodies

Drug	Bamlanivimab (Eli Lilly)	REGEN-COV (Regeneron)	Bamlanivimab / Etesevimab (Eli Lilly)
Trial	BLAZE-1[1] (Ph2 interim results) Arms (1:1:1:1) N=452 • Bam 700 mg, Bam 2800 mg, Bam 7000 mg, placebo	2067[2] (Phase 1-3 interim results) Arms (1:1:1) N=799 • REGEN-COV 2.4g, REGEN-COV 8g, placebo	BLAZE-1[3] (Ph3) Arms: (1:1) N=1035 • Bam 2800mg/ete 2800mg, placebo
Primary Endpoint	**D11 change in log viral load** 2800mg arm: −0.53 versus placebo p= 0.02	**D7 change in log viral load** Pooled treatment group = -0.36 P <0.0001	**Hospitalizations/death D29** **~70% relative reduction** vs. placebo 2.1% (11/517) vs. 7% (36/518) p= 0.0004 Death: 10/518 placebo, 0/517 bam/ete
Secondary Endpoint	**Hospitalizations/ER visits** High risk patients (pooled)= **~70% relative reduction** vs. placebo 4% (4/95) vs. 15% (7/48) placebo	**Medically attended visits** High risk patients (pooled)= **~70% relative reduction** vs. placebo 3% (4/151) vs. 9% (7/78) placebo	Viral load and symptom decrease all significant
Status	EUA (November 9, 2020): Bam 700 mg; high risk outpatients based on potential to decrease hospitalizations	EUA (November 21, 2020): REGEN-COV 2.4g; high risk outpatients based on potential to decrease hospitalizations	EUA (February 9, 2021); bam 700/ete 1400; high risk outpatients based on potential to decrease hospitalizations

1. https://www.nejm.org/doi/full/10.1056/NEJMoa2029849, https://www.fda.gov/media/143603/download
2. https://www.nejm.org/doi/full/10.1056/NEJMoa2035002?query=recirc_curatedRelated_article, https://www.fda.gov/media/145611/download
3. https://www.fda.gov/media/145802/download

mAbs Under EUA Recent Data: Treatment

Drug	Bamlanivimab / Etesevimab	Bamlanivimab / Etesevimab	REGEN-COV
Trial	BLAZE-1[1] (Ph2 final results) Arms: (1:1:1:1), (1:1) N=577 • Bam 700 mg, 2800 mg, 7000 mg, placebo • Bam 2800mg/ ete 2800mg, placebo	BLAZE-1[2] (Ph3) Arms: N=769 • Bam 700mg/ete 1400mg, placebo	2067 (Ph3) Arms: N=4567 • REGEN-COV 1200mg, 2400mg, placebo
Primary Endpoint	**D11 change in viral load** Combo arm: −0.57; p=0.01	**Hospitalizations/death D29** **87% relative reduction vs. placebo** 0.8% (4/511) vs. 5.9% (15/258) P <0.0001 Death: 4/258 placebo, 0/511 bam/ete	Hospitalizations/death D29 **~70% relative reduction vs. placebo** 1200mg: 1% (7/736) vs. 3.2% (24/748); p=0.0024 2400mg: 1.3% (18/1355) vs. 4.6% (62/1341); p<0.0001
Secondary Endpoint	**Hospitalizations/ER visits** High risk patients ~70% relative reduction Pooled mono= 4% (4/101), Combo= 0% (0/31) placebo= 13.5% (7/52)	Secondary endpoints including viral load all significant	Time to symptom resolution: median 4 day reduction; p<0.0001

1. https://jamanetwork.com/journals/jama/fullarticle/2775647
2. https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced
3. https://newsroom.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody

mAbs Recent Data: Post-exposure prophylaxis

Drug	REGEN-COV	Bamlanivimab
Trial	Phase 3 prevention[1] (interim) Arms: (1:1) N=400 • REGEN-COV 2.4g SQ • placebo	BLAZE-2[2] (post-exposure prophylaxis in LTCF) Arms: (1:1) N=299 • Bam 4200mg, placebo
Primary Endpoint	**Symptomatic infection** 8/223 placebo vs. 0/186 REGEN-COV **Symptomatic and asymptomatic** 23/223 placebo vs. 10/186 REGEN-COV	**Prevention of symptomatic COVID-19** OR=0.2; p=0.00026 80% relative reduction for residents

1. https://investor.regeneron.com/news-releases/news-release-details/regeneron-reports-positive-interim-data-regen-covtm-antibody
2. https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented

Future considerations for COVID-19 therapeutics

1. Implications of COVID-19 variants on mAbs
2. Therapies in development

SARS-CoV2 variants

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies

Certain variants have shown reduced susceptibility to **bamlanivimab alone** in in vitro studies[1]

Lineage with Spike Protein Substitution	Key Substitutions Tested[2]	Fold Reduction in Susceptibility
B.1.1.7 (UK)	**N501Y**	No change
B.1.351 (South Africa)	**E484K**	>2,360[3]
P.1 (Brazil)	**E484K**	>2,360[3]
B.1.427/B.1.429 (California)	**L452R**	>1,020[3]
B.1.526 (New York)[4]	**E484K**	>2,360[3]

- FDA Fact Sheets recently updated antiviral resistance **section 15** (bamlanivimab, bamlanivimab with etesevimab, and casirivimab with imdevimab)
- FDA Centers for Drug Evaluation and Research statement
- CDC updates on proportions of variants of concern by state

1. FDA factsheets: https://www.fda.gov/media/143603/download https://www.fda.gov/media/145802/download https://www.fda.gov/media/145611/download
2. For variants with more than one substitutions of concern, only the one with the greatest impact of activity is listed
3. No activity was observed at the highest concentration tested. Bamlanivimab alone is unlikely to be active against variants from this lineage
4. Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021)

SARS-CoV2 variants impact on mAb distribution

- Given the sustained increase in variants resistant to **bamlanivimab alone**, and availability of alternative authorized monoclonal antibodies, the USG, in coordination with Eli Lilly, will **stop the distribution of bamlanivimab alone starting today**

- All sites will continue to be able to **order bamlanivimab with etesevimab, etesevimab alone to pair with bamlanivimab on hand, or REGEN-COV** following existing ordering / reporting procedures

- To guide treatment decisions, healthcare providers should:
  - Review the **Antiviral Resistance information in Section 15 of the authorized Fact Sheets**[1] for each mAb therapy availed under EUA for details regarding specific variants and resistance
  - Refer to the **CDC website** (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from **state and local health authorities** regarding reports of viral variants of importance in their region

1. FDA factsheets: https://www.fda.gov/media/143603/download https://www.fda.gov/media/145802/download https://www.fda.gov/media/145611/download

Types of COVID-19 therapeutics in development

- nAbs
  - AZD7442, VIR-7831[1], Brii-196 & Brii-198, SAB-185
- Small molecule antivirals
  - molnupiravir[2]
- Immune modulators
  - MK-7110, cenicriviroc, lenzilumab
- Anticoagulants
- Repurposing approved drugs

➢ “Long COVID”[3]

1. 1https://investors.vir.bio/news-releases/news-release-details/vir-biotechnology-and-gsk-announce-vir-7831-reduces
2. https://www.merck.com/news/ridgeback-biotherapeutics-and-merck-announce-preliminary-findings-from-a-phase-2a-trial-of-investigational-covid-19-therapeutic-molnupiravir/
3. https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-covid


DEPARTMENT OF HEALTH & HUMAN SERVICES
USA


DEPARTMENT OF DEFENSE
UNITED STATES OF AMERICA

Thank you!