Got anything for the Cough?
Treatments for Early COVID-19

Davey Smith, MD
Chief, Division of Infectious Diseases and Global Public Health
Florence Seeley Riford Chair of AIDS Research
Professor of Medicine, University of California San Diego

This activity is jointly provided by Physicians’ Research Network and the Medical Society of the State of New York.
Got anything for this cough?

- Disclosures
- Bayer, Arena Pharmaceuticals,
- Kiadis Pharmaceuticals,
- Safe Aloha,
- FluxErgy,
- Linear Therapies,
- Protocol Co-Chair for ACTIV-2
590+ Drug development programs in planning stages

400+ Trials reviewed by FDA

9 COVID-19 treatments currently authorized for Emergency Use

1 Treatment currently approved by FDA for use in COVID-19

Courtesy of A. Chaillon
Adapted from FDA
Natural History

Exposure

No Symptoms  Mild  Moderate  Severe

BMJ 2020;371:m3862 - Courtesy of A. Chaillon
When to treat and what to use

- **Immunomodulators**
- **Antivirals**

**Viral Load**

- Exposure
- No Symptoms
- Mild
- Moderate
- Severe

**Antivirals**

*BMJ 2020;371:m3862 - Courtesy of A. Chaillon*
When to treat and what to use

**Immunomodulators**

**Antivirals**

Viral Load

Exposure

Inflammation

No Symptoms  Mild  Moderate  Severe

Antivirals

*BMJ* 2020;371:m3862 - Courtesy of A. Chaillon
When to treat and what to use

Exposure → Viral Load → Inflammation

- No Symptoms
- Mild
- Moderate
- Severe

Antivirals

Immunomodulators

*BMJ 2020;371:m3862 - Courtesy of A. Chaillon*
This Talk Will Focus On Antivirals

Exposure

Viral Load

No Symptoms  Mild  Moderate  Severe

Antivirals

BMJ 2020;371:m3862 - Courtesy of A. Chaillon
HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine. The FDA has moved mountains - Thank You! Hopefully they will BOTH (H works better with A, International Journal of Antimicrobial Agents).....
1st Nobel Prize: Diphtheria

Scientists grow diphtheria-causing bacteria in the laboratory and harvest its toxin. Next, researchers inject horses with the diphtheria toxin. As an immune response, the animals' blood produces diphtheria antitoxin. Scientists collect blood from the horses and separate out the antitoxin rich serum. Then, researchers purify the antitoxin serum for use as a medicine for people.

Passive Antibody Infusion Treated Children with Diphtheria

Convalescent plasma

How does convalescent plasma therapy work?

1. Blood is collected and run through a machine to separate antibody-containing plasma in a process called apheresis.

2. Convalescent plasma is collected and the rest of the blood is returned to the donor’s body.

Transfusion

Antibody

Plasma collection

Apheresis

Blood collection

Blood return
Convalescent plasma

- Convalescent plasma used w/in 72 hours in 165 elderly persons (+75yo) or 65-74yo with comorbidities with COVID-19
- NNT to avert one episode of severe resp illness was 7.

Libster et al. NEJM. Jan 6, 2021.
Convalescent plasma

- Multicenter study of CP in hospitalized patients with +PCR
- CP donors had high NAb levels
- Participants also often had high NAb at enrollment
- Stopped after 86 participants for futility.

Jordans et al CROI 2021 Late breaker abstract 120.
Monoclonal antibodies

Developed from people who caught the virus
Monoclonal antibodies

Developed from people who caught the virus

Purified and expanded

Turned into a treatment
Monoclonal antibodies

Developed from people who caught the virus

Purified and expanded

Turned into a treatment

To then treat other people with the virus

- >25 Companies have made MAbs that are in various stages of clinical testing.
Casirivimab and imdevimab

- **Viral Loads**
  - 275 patients randomized 1:1:1 to receive 8 g cocktail (n=90), 2.4 g cocktail (n=92) or placebo (n=93).

- **Viral Load over time in the overall population**

  ![Graph showing viral load over time with differences from baseline, day 7](image)

  - Difference in Change from Baseline, Day 7
    - TWA LS mean
    - Mean
    - 2.4 g vs. Placebo: -0.25, -0.72
    - 8.0 g vs. Placebo: -0.56, -0.74

- **No. at Risk**
  - Placebo: 81, 70, 78, 78
  - REGN-COV2, 2.4 g: 73, 66, 69, 70
  - REGN-COV2, 8.0 g: 74, 70, 73, 73

Weinreich et al. NEJM Dec 2020.
Viral Loads

- 275 patients randomized 1:1:1 to receive 8 g cocktail (n=90), 2.4 g cocktail (n=92) or placebo (n=93).

President Trump was treated with this
Bamlanivimab (LY-CoV555)

- Symptom scores
  - 452 persons received LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo

![Graph showing change in symptom scores from baseline over trial days]

**Delta Value (95% CI)**
- Day 2: -0.79 (-1.35 to -0.24)
- Day 3: -0.57 (-1.12 to -0.01)
- Day 4: -1.04 (-1.60 to -0.49)
- Day 5: -0.73 (-1.28 to -0.17)
- Day 6: -0.79 (-1.35 to -0.23)
- Day 7: -0.50 (-1.06 to 0.07)
- Day 8: -0.65 (-1.28 to -0.02)
- Day 9: -0.15 (-0.75 to 0.45)
- Day 10: -0.32 (-0.94 to 0.29)
- Day 11: -0.44 (-1.02 to 0.15)

Bamlanivimab (LY-CoV555)

- **Symptom scores**
  - 452 persons received LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo

---

**Delta Value (95% CI)**

<table>
<thead>
<tr>
<th>Trial Day</th>
<th>Delta Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>-0.79 (-1.35 to -0.24)</td>
</tr>
<tr>
<td>Day 3</td>
<td>-0.57 (-1.12 to -0.01)</td>
</tr>
<tr>
<td>Day 4</td>
<td>-1.04 (-1.60 to -0.49)</td>
</tr>
<tr>
<td>Day 5</td>
<td>-0.73 (-1.28 to -0.17)</td>
</tr>
<tr>
<td>Day 6</td>
<td>-0.79 (-1.35 to -0.23)</td>
</tr>
<tr>
<td>Day 7</td>
<td>-0.50 (-1.06 to 0.07)</td>
</tr>
<tr>
<td>Day 8</td>
<td>-0.65 (-1.28 to -0.02)</td>
</tr>
<tr>
<td>Day 9</td>
<td>-0.15 (-0.75 to 0.45)</td>
</tr>
<tr>
<td>Day 10</td>
<td>-0.32 (-0.94 to 0.29)</td>
</tr>
<tr>
<td>Day 11</td>
<td>-0.44 (-1.02 to 0.15)</td>
</tr>
</tbody>
</table>

Bamlanivimab (LY-CoV555)

- Nursing Home BLAZE-2 Prevention Study

Cohen et al CROI 2021 Late breaker abstract 121.
Bamlanivimab + Etesevimab

Figure 2. Change in Log Viral Load and in Viral Load Cycle Threshold Over Time With Bamlanivimab Monotherapy and Bamlanivimab and Etesevimab Combination Therapy

Viral Load change from baseline

# Covid-19 Related Hospitalization or Death by Any Cause by Day 29

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Rate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>517</td>
<td>36</td>
<td>7.0%</td>
<td>-</td>
</tr>
<tr>
<td>Bamlanivimab 2800 mg + Etesevimab 2800 mg</td>
<td>518</td>
<td>11</td>
<td>2.1%</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

70% reduction vs. placebo

# Death by Any Cause by Day 29

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>517</td>
<td>10*</td>
<td>1.9%</td>
</tr>
<tr>
<td>Bamlanivimab 2800 mg + Etesevimab 2800 mg</td>
<td>518</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

No deaths of any cause with antibody therapy
# Bamlanivimab + Etesevimab

**EUA**

## COVID-19 RELATED HOSPITALIZATION OR DEATH BY ANY CAUSE BY DAY 29

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Rate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>517</td>
<td>36</td>
<td>7.0%</td>
<td>-</td>
</tr>
<tr>
<td>Bamlanivimab 2800 mg + Etesevimab 2800 mg</td>
<td>518</td>
<td>11</td>
<td>2.1%</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

![70% reduction vs. placebo](https://via.placeholder.com/150)

**NIH guidelines**

## DEATH BY ANY CAUSE BY DAY 29

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>517</td>
<td>10*</td>
<td>1.9%</td>
</tr>
<tr>
<td>Bamlanivimab 2800 mg + Etesevimab 2800 mg</td>
<td>518</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

No deaths of any cause with antibody therapy

Lily Press Release Jan 26, 2021
Mab Therapy

- **Present**
  - Only for high-risk persons with early COVID-19
  - **Not** for 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

- **Future**
  - New routes: IM, SQ, Inhaled
  - EUA ≠ Approval
  - FDA explicitly encouraged more research before approval
CoV-2 Evolves to its New Home

- Among RNA, coronaviruses have modest mutation rate
- Example D614G in Spike
  - Increased infectivity
  - Increased transmissibility in animal models

\[
\begin{array}{cccc}
614 & \text{Virus 1: } & D & R \ \ D \ A \ V \ E \ Y \ S \ M \ I \ T \ H \\
& \text{Virus 2: } & D & R \ G \ A \ V \ E \ Y \ S \ M \ I \ T \ H \\
\end{array}
\]
CoV-2 Evolves to its New Home

- Among RNA, coronaviruses have modest mutation rate
- Example D614G in Spike
  - Increased infectivity
  - Increased transmissibility in animal models

Virus 1: D R D A V E Y S M I T H
Virus 2: D R G A V E Y S M I T H

Magnitude of Infection

CoV-2 Evolves to its New Home

Virus 1: D R D A V E Y S M I T H
Virus 2: D R G A V E Y S M I T H

• Neutralization by 14 of the 17 most potent mAbs tested was reduced or abolished by either K417N, or E484K, or N501Y mutations.

Wang et al. BioRx doi: https://doi.org/10.1101/2021.01.15.426911
Do Variants Impact mAb Treatments?

Original virus (black), 1Y.V2 (red), or a chimeric construct that includes only the RBD mutations **K417N, E484K, and N501Y** (maroon)

Wang et al. BioRx doi: https://doi.org/10.1101/2021.01.15.426911
Do Variants Impact mAb Treatments?

- **Rationale**
  - Ab cocktails likely to have better efficacy against new variants.
  - Non-infusion likely will have better uptake
# VoC overview (February 2021)

<table>
<thead>
<tr>
<th>Names</th>
<th>Notable mutations</th>
<th>Origin</th>
<th>Consequences (examples)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>20I/501Y.V1, VOC 202012/01, B.1.1.7</td>
<td>N501Y (17 mutations total)</td>
<td>U.K.</td>
<td>Increased binding affinity potential increased lethality</td>
<td>(Rambaut, Loman, Pybus et al. 2020, Public Health England 2021)</td>
</tr>
<tr>
<td>20A.EU1, B.1.177</td>
<td>A222V</td>
<td>Spain</td>
<td>Increased transmissibility Reinfec­tion?</td>
<td>(Hodcroft, Zuber, Nadeau et al. 2020, To, Hung, Ip et al. 2020)</td>
</tr>
<tr>
<td>L452R variant</td>
<td>L452R</td>
<td>California</td>
<td>Escape to mAbs X593 and P2B-2F6</td>
<td>(Li, Wu, Nie et al. 2020)</td>
</tr>
</tbody>
</table>
Cows: polyclonal antibodies

EIDD 2801/MK4482 (Molnupiravir)

- Orally bioavailable ribonucleoside analog
- Activity against various unrelated RNA viruses: influenza, Ebola, CoV, Venezuelan equine encephalitis virus
- Lethal mutagenesis

https://www.nature.com/articles/s41564-020-00835-2
EIDD 2801/MK4482 (Molnupiravir)

https://www.nature.com/articles/s41564-020-00835-2
EIDD 2801/MK4482 (Molnupiravir)

- NP swabs analyzed from 175 participants at enrollment, Day 3, and Day 5 for SARS-CoV-2 infectivity.

CROI Latebreaker: Painter et al
Camostat Mesilate

- Serine protease inhibitor that is orally dosed and blocks TMPRSS2
- Inhibits SARS-CoV-2 in vitro
- Approved for clinical use in Japan since 1985 for pancreatitis

Hoffmann, Cell 2020
Inhaled Interferon β

In vitro

Li, J. et al. Virus Res 2020; 286:198074
Mantlo, E. et al Antiviral Res 2020; 179:104811
Inhaled Interferon β

**In vitro**

- Li, J. et al. Virus Res 2020; 286:198074
- Mantlo, E. et al Antiviral Res 2020; 179:104811

**In vivo**

- RCT of hospitalized patients with COVID-19 (n=98)

Inhaled Interferon β

**In vitro**

- Bars representing viral titer (TCID\(_{50}\)/ml) at different doses (IU/ml) for IFN-α and IFN-β.
- Among doses 5-50 IU/ml, IFN-β shows a dosedependent decrease in viral titer compared to IFN-α.

**In vivo**

- Bars representing recovery and outcomes for hospital discharge and better outcomes.
- ITT analysis for different outcomes.

RCT of hospitalized patients with COVID-19 (n=98)

Li, J. et al. Virus Res 2020; 286:198074
Mantlo, E. et al Antiviral Res 2020; 179:104811
COLCORONA Trial

- Colchicine (0.5 mg BID x 3d then QD x27 days thereafter)
- 4159 participants with PCR+ and COVID-19 with at least 1 high risk criteria
- Primary endpoint: composite hosp and death
- 4.7% in colchicine group and 5.8% in placebo group (P=0.08)

- Stopped early for convenience
- Not an antiviral

Summary

- Antivirals are being developed for SARS-CoV-2
- Ab-based therapies are promising and have gotten EUAs
- Currently only available by IV (new versions coming)
- Maybe thwarted by viral evolution
- Serine protease inhibitors, viral polymerase inhibitors, Interferon and others are in trials

- Check out ACTIV-2 (www.riseabovecovid.org)
Question #1

- Treatment for what pathogen won the first Nobel Prize in Medicine in 1901?
  - Influenza
  - Coronavirus
  - Streptococcus pyogenes
  - Measles
  - Corynebacteria diptheriae

Passive immunization using horses was used to treat diptheria in children
Question #2

• What type of treatment for COVID-19 is Bamlinivimab?
  • Protease inhibitor
  • **Monoclonal antibody**
  • RNA polymerase inhibitor
  • Immunomodulator
  • Anticoagulant

Bam is a monoclonal antibody that received EUA for treatment of early COVID-19
Question #3

What type of treatment for COVID-19 is Camostat mesilate?

- **Protease inhibitor**
- Monoclonal antibody
- RNA polymerase inhibitor
- Immunomodulator
- Anticoagulant

Camostat is a protease inhibitor that aims to block a human serine protease that SARS-CoV-2 needs in its life cycle.
Question #4

• What treatment did President Trump receive when he got COVID-19?
  • Camostat
  • Casirivimab
  • Molpunavir
  • Hydroxychloroquine
  • Azithromycin
  • All the above

Casi is a monoclonal antibody that President Trump received as part of a cocktail for treatment of his COVID-19.
Question #5

• Who is eligible for monoclonal antibody treatment under EUA?
  • 66 year old woman with +SARS-CoV-2 PCR but no symptoms. She has a BMI of 30 but no co-morbidities
  • 66 year old woman with +SARS-CoV-2 PCR with mild cough starting two days before. She has no co-morbidities but lives with husband who is diabetic.
  • 66 year old man with diabetes and exposed his wife who has a +SARS-CoV-2 PCR but his PCR was negative.
  • 86 year old man with +SARS-CoV-2 PCR hospitalized with COVID-19 pneumonia and has cough but not requiring oxygen.
  • **86 year old man with no comorbidities +SARS-CoV-2 PCR with mild fatigue starting two days before.**
Question #5

- Who is eligible for monoclonal antibody treatment under EUA?
  - 86 year old man with no comorbidities + SARS-CoV-2 PCR with mild fatigue starting two days before.

**EUA monoclonal antibody is for treatment of COVID-19 in people who are at high risk of disease progression (older and co-morbidities) and not already hospitalized.**
ACKNOWLEDGEMENTS

- ACTIV-2 Participants, Study Team
- US Govt Response to COVID-19
- Antoine Chaillon
- CROI 2021
Thank You for Your Attendance!

Please visit us at:

www.prn.org