Current and Future Treatments for COVID-19

Michael P. Veve, PharmD, MPH
Assistant Professor, UTHSC College of Pharmacy
Knoxville, Tennessee
Disclosures

• I have received funding or served on an advising council for the following entities:
  - Paratek Pharmaceuticals
  - Cumberland Pharmaceuticals
  - Summit Therapeutics

• There are no Food and Drug Administration-approved therapies for treatment of COVID-19.
Objectives

i. Identify therapies currently explored as treatment options in COVID-19.

ii. Understand some of the literature supporting or refuting these treatment options for COVID-19.
Coronavirus Disease 2019: A Public Health Pandemic

- United States = Highest cases/death

- Progression to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
  - Low O$_2$ saturation, mechanical ventilation, extracorporeal membrane oxygenation

- Several currently available drugs repurposed

COVID-19 Structure

i. Envelope

ii. Spike glycoprotein

iii. Membrane protein

iv. Nucleocapsid protein with RNA

v. Envelope Protein

COVID-19 Lifecycle

Antibodies

ACE2 Receptor

Protein Synthesis

Replication

Hydroxychloroquine + Antivirals

Antivirals

NFkB

IFNs

IL1, IL6, TNF

Cytokine Receptor

IFNAR

TLR

Interleukin Inhibitors, Corticosteroids

JAK Inhibitors

COVID-19 Lifecycle

- Antibodies
- ACE2 Receptor
- Hydroxychloroquine + Antivirals
- Protein Synthesis
- Antivirals
- Replication
- NFkB
- IL1, IL6, TNF
- IFNs
- TLR
- Cytokine Receptor
- Interleukin Inhibitors, Corticosteroids
- JAK Inhibitors
- IFNAR

“Promising* Therapies” in COVID-19

*Emphasized caution on the word promising
Remdesivir (GS-5734)

- **Mechanism:**
  - Interferes with viral RNA-dependent RNA polymerase; delayed chain termination of viral RNA transcription

- **Dosing and Pharmacokinetics**
  - 200mg IV x1, then 100mg IV daily for 5-10 days
  - Variable renal elimination, 12% protein bound

- **Safety Outcomes**
  - CYP interactions?, AST/ALT increases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lancet Severe RCT</th>
<th>ACTT-1</th>
<th>SIMPLE-1 Severe</th>
<th>SIMPLE-2 Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample, (n)</td>
<td>237</td>
<td>1063</td>
<td>397</td>
<td>596</td>
</tr>
<tr>
<td>Severity</td>
<td>Hypoxia, PNA or P/F &lt;300</td>
<td>Hypoxia/PNA/ Suppl’ O₂</td>
<td>PNA/Hypoxia, No MV</td>
<td>SpO₂ ≥ 94%</td>
</tr>
<tr>
<td>Sx duration, days (IQR)</td>
<td>10 (9-12)</td>
<td>9 (6-12)</td>
<td>8 (5-11)</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Intervention</td>
<td>10-day PBO</td>
<td>10-day PBO</td>
<td>5-day 10-day</td>
<td>10-day 5-day SOC</td>
</tr>
<tr>
<td>28-day Mortality, (%)</td>
<td>14</td>
<td>13</td>
<td>7.1</td>
<td>8</td>
</tr>
<tr>
<td>TTCR (days) / Recovery (%)</td>
<td>21 days</td>
<td>23 days</td>
<td>11 days</td>
<td>10</td>
</tr>
<tr>
<td>AEs &amp; Discontinued Therapy, n (%)</td>
<td>18 (12)</td>
<td>4 (5)</td>
<td>36 (6.7)</td>
<td>8 (4)</td>
</tr>
</tbody>
</table>

Key: Sx, symptoms; TTCR, time to clinical recovery; AE, adverse event; PNA, pneumonia; P/F, arterial oxygen partial pressure to fractional inspired oxygen; PBO, placebo; MV, mechanical ventilation; SpO₂, oxygen saturation; SOC, standard of care; N/A, not applicable

Table adapted from Matt Davis, PharmD; Wang Lancet 2020; Beigel NEJM 2020; Goldman NEJM 2020; Spinner JAMA 2020
Summary: Remdesivir

- Clinical trial data conflicting to date
  - Reduced time to clinical recovery, questionable mortality data
  - Selection bias, confusing endpoints, underpowered studies

- Theoretical benefit early in disease progression
  - Limited effect as viral replication is maximized
  - At least 8 clinical trials on-going

- Well-tolerated
Convalescent Plasma

- **Mechanism**
  - Adaptive immunity to passive immunity

- **Dosing**
  - 1 to 2 units (~200 mL/unit)

- **Contingent on matching**
  - Standardization of donor pool
  - Adverse effect profile?

Donors Recovered from COVID-19

SARS-CoV-2 Neutralizing Anti-bodies

Plasma Donation

Patients with COVID-19

Major Clinical Trial: Convalescent Plasma

- **PLACID Trial**
  - Multicenter, randomized Phase II trial
  - Hospitalized, moderately ill COVID-19 + patients
  - SOC ($n=235$) vs SOC + convalescent plasma $\times$ two doses ($n=229$)

- **No association with disease progression OR 28-day mortality**
  - 17.9% SOC, 18.7% SOC + convalescent plasma
  - adjOR: 1.09; 95% CI: 0.67, 1.77

Summary: Convalescent Plasma

- **Unknown clinical benefit**
  - Mortality or time to death
  - Symptomatic improvement

- **Unclear benefit of second transfusion**

- **No firm recommendations for use**
  - Need for donor pool potency

Cochrane Review of 20 studies + >5400 patients

Corticosteroids

• **Mechanism**
  - Anti-inflammatory/immunomodulatory agent
  - Reduce pro-inflammatory compounds (i.e., cytokines)

• **Dosage:** dexamethasone 6 mg/day for 10 days

• **Adverse effect profile**
  - Potential drug-drug interactions
  - Dysglycemia, mood changes, weight gain

---

Major Clinical Trial: Corticosteroids

• RECOVERY Trial
- Multicenter, open-label adaptive trial in United Kingdom
- Hospitalized, severely ill COVID-19 + patients
- SOC ($n=4,321$) vs SOC + dexamethasone ($n=6,425$)
  - Very few patients received other anti-COVID therapies

• Significant reduction in 28-day all-cause mortality
  - 25.7% SOC, 22.9% SOC + dexamethasone
  - adjOR: 0.83; 95% CI: 0.75-0.93

Summary: Corticosteroids

• Results from RECOVERY suggests mortality benefit in critically ill patients with SARS-CoV-2
  - Mechanical ventilation or requiring supp’l O2
  - No supp’l O2, No benefit
• Several supportive observational studies
  - Reduced mortality, improved oxygenation, need for mechanical ventilation, hospital or ICU LOS
• Potentially a class effect?

Therapies Lacking Evidence for Use in COVID-19
Hydroxychloroquine (+/- Azithromycin)

• Proposed Mechanism:
  - Interference with viral cell entry and replication

• False inferences from small observational patients

• Several conflicting observational data
  - Henry Ford Hospital data confounded by corticosteroid use

Interleukin (IL) Inhibitors

- **Tocilizumab, sarilumab, siltuximab**
  - Recombinant monoclonal antibodies
  - Unclear ideal dosing regimens

- **Potential Role: Cytokine-storm syndrome**
  - Adverse events: neutropenia, thrombocytopenia, liver injury

- **Clinical Trials suggest unsuitable for COVID-19 treatment**
  - Sarilumab clinical trial failed to meet clinical endpoints

---

Therapy-attributed Adverse Effects

- “Do no harm”

- Cardiac arrhythmias, increased death
  - QTc prolonging potential
  - Increased with azithromycin

- Prolonged immunosuppression
  - Increased risk of secondary infections while hospitalized

Mercuro NJ, et al. JAMA Cardiol. 2020;e201834.
Other Uninspiring COVID-19 Therapies Not Covered in this Presentation

<table>
<thead>
<tr>
<th>Other Experimental COVID-19 Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
</tr>
<tr>
<td>Zinc</td>
</tr>
<tr>
<td>Immunoglobulins</td>
</tr>
<tr>
<td>ACEi/ARB</td>
</tr>
<tr>
<td>Olseltamivir</td>
</tr>
<tr>
<td>Baloxovir</td>
</tr>
<tr>
<td>Nitazoxanide</td>
</tr>
<tr>
<td>Ribavirin</td>
</tr>
<tr>
<td>Kinase Inhibitors</td>
</tr>
<tr>
<td>Interferons</td>
</tr>
<tr>
<td>IL-1 Inhibitors</td>
</tr>
<tr>
<td>Other Protease Inhibitors</td>
</tr>
</tbody>
</table>

Future Directions for COVID-19 Treatment or Prevention
Favipiravir

• **Mechanism**
  - RNA-dependent RNA polymerase (RdRp) inhibitor

• *In vivo* data suggest activity towards SARS-CoV-2
  - Favipiravir ($n=116$) vs umifenovir ($n=120$)
  - Higher rate of clinical recovery at 7 days (71% vs 56%)

• Several RCTs on-going

COVID-19 Vaccine Candidates

• 211 vaccine candidates in development

• Successful neutralizing titers for several products

Summary: Vaccines in Clinical Trials

• “When will we get a vaccine”?

• Politicization of vaccine/clinical trials
  - Fast tracking
Take Home Points

• Bad science has plagued us, too

• The jury is still out on some agents, others not so much

• Public health/vaccines = better investment in time and resources?
Looking for more COVID-19 Resources? Visit the Society of Infectious Diseases Pharmacists webpage: https://sidp.org/covid19
Other Resources

• Contagion Live
  - https://www.contagionlive.com/disease-specific-topics/coronavirus

• National Institutes of Health (NIH)

• Centers for Disease Control and Prevention (CDC) or World Health Organization (WHO) guidance
Assessment Question:
Which of the following therapies has the highest level of evidence to support a decrease in all-cause mortality for SARS-CoV-2 infections?

i. Dexamethasone
ii. Convalescent plasma
iii. Hydroxychloroquine
iv. Remdesivir
Current and Future Treatments for COVID-19

Michael P. Veve, PharmD, MPH
Assistant Professor, UTHSC College of Pharmacy
Knoxville, Tennessee