Special Session on COVID-19 Therapeutics

will begin at

1 pm ET/12 pm CT/11 pm MT/10 am PT
Special Session on COVID-19 Therapeutics
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COVID-19 Therapeutics
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• Disclosures
  – Johnson and Johnson (equity holder)
Illness Phases/Approaches

Figure: Schematic of clinical course of severe COVID-19 with representation of SARS-CoV-2 RNA levels, common symptoms, and possible timing of therapeutic use of greatest benefit.
How many drug intervention trials for COVID-19?

Clinicaltrials.gov (5/14/2020)
Many approaches/SARS-CoV-2

So much “promise,”

...so little to show

**SAR-CoV-2**

Hydroxychloroquine
Chloroquine
Ivermectin
Lopinavir/ritonavir

Favipiravir
Baloxivir
Indomethacin
Zinc
Vitamin C
Famotidine

Viral Tissue Culture studies, *in vitro*

≠

Human studies, *in vivo*
Early opinions shaped by Chinese COVID-19 Guidelines

- Hydroxychloroquine or chloroquine
- Lopinavir/ritonavir
- Oseltamivir, favipiravir or umifenovir
- Tocilizumab
- Traditional Chinese medicine

- Many used in combination based on limited data (in vitro), expert opinion, case series
Remdesivir: Antiviral

Remdesivir
Potential repurposed drug for COVID-19

SARS-CoV-2

ACE2 receptor

Ribosome

RdRp

Translation of viral polymerase protein (RdRp)

Inhibition of RNA replication

Cytoplasm

Remdesivir (Prodrug)

GS-441524 (Active molecule)

Genomic replication
Subgenomic (nested) transcription
Nucleocapsid (N)
Spike (S)
Membrane (M)
Envelope (E)

RdRp SARS-CoV-2
PDB ID: 6M71

GS-441524 binding pocket
RDV: why is this trial in NEJM?

- 61 pts, open label, no comparator
- 40 (75%) had 10d course
- 34 (69%) mechanical ventilation
- Majority had co-morbidities

- At d18, 68% had improved oxygenation
- At time of writing
  - 47% discharged
  - 13% died
- Usual range if in ICU, ventilated 20-40%?

- No conclusions possible from this case series
- 23% had severe side effects
Remdesivir in Adults w/ Severe COVID-19: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

- N = 237 patients, halted
- Confirmed infection, 12 days or fewer of symptoms, lung involvement
- Remdesivir 200 mg day 1, then 100 mg IV daily vs placebo

Findings:
- No clinical improvement (subgroup <10 days with trend)
- No difference in mortality (subgroup <10 days with trend)
- No effect on viral load in upper or lower respiratory tracts

Adaptive COVID-19 Treatment Trial (ACTT): Remdesivir

• Sponsor: NIAID/NIH
• RCT: Remdesivir vs placebo (began 2/21/20)
• N = 1063 patients, 68 sites (47 in US; 21 from Europe and Asia)

Preliminary results
• Remdesivir pts 31% faster time to recovery than those who received placebo ($P < 0.001$)
• Median time to recovery: 11 days remdesivir vs 15 days placebo
• Survival benefit? trend
  – Mortality rate 8.0% remdesivir vs 11.6% placebo group ($P = 0.059$)

Accessed April 29, 2020
• Awaiting more analysis
• Trial is adapting—starting mid May
  – RDV v. RDV plus baricitinib
    • JAK1/JAK2 subtype inhibitor, interferes w/ signal transduction STAT proteins, stopping gene expression in immunomodulatory cells
RDV Distribution Issues

5/12: RDV under FDA EUA—“Still an investigational drug”
US Government now Shipping to state health departments
Open-label, randomized, phase 2 trial

Hong Kong, (2:1) 14-day

- Combination: lopinavir 400 mg/ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate day
- lopinavir 400 mg and ritonavir 100 mg every 12 h (control group)
- primary endpoint was the time to providing a nasopharyngeal swab negative
• 127 patients, 86 combination/41 control
• Median days symptom onset 5 days (IQR 3–7)
• Combination group
  – Reduced viral carriage x 5 days
    • Negative nasopharyngeal swab (7 days [IQR 5–11]) v. control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], p=0.0010)
  – Faster alleviation of symptoms x 4 days
    • NEWS2 of 0 (4 days [IQR 3–8] in the combination group vs 8 days [7–9] in the control group; HR 3.92 [95% CI 1.66–9.23], p<0.0001)
    – Adverse events included self-limited nausea and diarrhea with no difference between the two groups.
• Need for larger study, true placebo arm
# Hydroxychloroquine (HCQ) and Chloroquine (CQ)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type (n)</th>
<th>Drug(s)</th>
<th>Viral carriage reduction</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao</td>
<td>Series (100) Mentioned in report</td>
<td>CQ, CQ</td>
<td>“superior”</td>
<td>Inhibits pneumonia, ↓ duration</td>
</tr>
<tr>
<td>Chen J</td>
<td>RCT (30)</td>
<td>HCCQ</td>
<td>86% (HCCQ), 93% (control)</td>
<td>None</td>
</tr>
<tr>
<td>Chen Z</td>
<td>RCT (62)</td>
<td>HCCQ</td>
<td>n/a</td>
<td>↓ fever x 1d, improved imaging</td>
</tr>
<tr>
<td>Gautret P</td>
<td>Non-RCT (36)</td>
<td>HCCQ, HCCQ+ AZ</td>
<td>Combination = ↓ shedding (6 pts)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gautret P</td>
<td>Non-RCT (90) mild dz</td>
<td>HCCQ+ AZ</td>
<td>80% with negative PCR d8 (no comparator arm)</td>
<td>N/A</td>
</tr>
<tr>
<td>Molina J</td>
<td>Non-RCT (11)</td>
<td>HCCQ + AZ</td>
<td>80% positive d5-6</td>
<td>1 death 1 QT prolonged</td>
</tr>
<tr>
<td>Borba M</td>
<td>RCT IIb (81)</td>
<td>CQ (high dose)</td>
<td>1/14 negative PCR (d4)</td>
<td>High dose = lethality trend (17%), low dose (13%)</td>
</tr>
</tbody>
</table>
25 hospitals, retrospective
N = 1438 patients

adjusted HR in-hospital mortality
HCQ 1.08
Azithromycin 0.56
HCQ + AZ 1.35

None were statistically significant
Growing Safety Concerns Regarding HCQ & CQ

- French National Agency for the Safety of Medicine and Health Products (ANSM, from 3/27/20 forward)
  - Pharmacovigilance surveys re: COVID-19
  - Sub-analysis, 43 of 53 cardiac adverse events occurred
    - Receiving HCQ or HCQ plus azithromycin
    - 7 cases cardiac death
    - 12 rhythm disorders \( \rightarrow \) syncope
    - All others, prolonged QT

- VA retrospective series (Magagnoli et al, 2020 pre-print)

<table>
<thead>
<tr>
<th>Table 5. Subdistribution hazard of ventilation, death and death after ventilation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Hazard Ratio (95% Confidence Interval)</td>
</tr>
<tr>
<td>Ventilation</td>
</tr>
<tr>
<td>HC</td>
</tr>
<tr>
<td>HC vs. No HC</td>
</tr>
<tr>
<td>HC+AZ</td>
</tr>
</tbody>
</table>

Drug studies: meta-analysis

• 155 “studies” evaluated (preprint or published)
• No double blind, placebo-controlled RCT of high quality
• Data neither to endorse or to refute use of HCQ or CQ

Fajgenbaum et al.  
https://www.medrxiv.org/content/10.1101/2020.05.07.20073981v1.full.pdf (pre-print, release 5/11/20)
COVID-19 Cytokine Storm

Multiple organs affected
Lungs
Kidneys
Brain
GI
Cardiac
Vasculature
CNS
Liver
Acute Respiratory Distress Syndrome (ARDS, bacterial sepsis or pneumonia)

Alveolar Changes

Healthy alveolus

- Healthy alveoli
- Normal air exchange
- No inflammation

Injured alveolus

- Alveolar macrophage
- Type II pneumocyte
- Type I pneumocyte
- Surfactant layer
- Fibrin
- Activated neutrophil
- Migrating neutrophil
- Platelets
- Inflamed endothelial cells
- Gap formation
- Widening of edematous interstitium
- Sloughing of damaged bronchial epithelium

Endothelial cell

RBC
SARS-CoV-2 lung injury

Likely similar to
Influenza-related ARDS

COVID-19: Effects on Vasculature

ACE2 receptors & virus --> clots, MIs

Thrombotic vasculopathy postulates
- Elevated D-Dimers & vWF antigen/activity
- Weibel-Palade bodies from endothelial cells
- ultralarge vWF multimers bind platelets, deposit in vessel walls and yield
- acquired ADAMTS13 deficiency, a TTP-like state
- Elevated levels of lupus anticoagulant --> change aPTT values
Clots, clots and more clots (selected papers)

- Italy, 388 pts, 68% men, 16% ICU
  - Prophylaxis 100% ICU, 75% on ward.
  - Thrombosis 21% (27.6% ICU, 6.6% ward).
  - 50% diagnosed in first 24h
  - Overt DIC in 8 (2.2%) [Lodigiani, Thromb Res 2020; 191:9-14]
- France, High incidence in fully anticoagulated patients
  ICU (n=26) 100% vs. 56% p=0.03 [Llitjos JF J Thromb Haemost 2020]
- Netherlands, high incidence thrombosis in ICU
  - N = 184, 31% incidence thrombotic complications [Klok, Thromb Res 2020, Apr 10]
- China, hospitalized patients
  - 19.7% of 416 pts, cardiac injury [Shi, JAMA Cardiology, 2020]

COVID-19

PLASMA & IMMUNOTHERAPIES
History of convalescent serum/plasma use

Post-exposure prophylaxis & treatment

- Hepatitis A
- Hepatitis E
- Polio
- Mumps
- Measles
- Rabies
- Ebola
- MERS-CoV
Convalescent plasma SARS-CoV-1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Good outcome</th>
<th>Poor outcome</th>
<th>P value</th>
<th>Logistic regression P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>33</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.9±12.5</td>
<td>50.2±15.1</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>Admission LDH (IU/l)</td>
<td>268.6±117.6</td>
<td>334±183.7</td>
<td>0.08</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean day of plasma infusion</td>
<td>11.7±2.3</td>
<td>16.0±6.0</td>
<td>&lt;0.001</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean plasma volume</td>
<td>253.6±99.9</td>
<td>297.23±141.4</td>
<td>0.11</td>
<td>0.174</td>
</tr>
<tr>
<td>PCR positive and seronegative for SARS</td>
<td>20</td>
<td>10</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Convalescent Plasma

- Convalescent plasma for Severe COVID-19
  - eIND from FDA (3/26/20)
  - Multiple trials: Treatment (early & late), prevention

Serum from recovered COVID-19 patients containing virus neutralizing antibodies can be infused into sick patients with the goal of reducing symptoms. (J Clin Invest. 2020. https://doi.org/10.1172/JCI138003)
Convalescent Plasma & COVID-19

• Possible mechanisms of action
  – Direct neutralization of the virus
  – Control of hyperinflammation
    • Impact similar to IVIG
    • Impact Th1/Th17 ratio, complement activation
  – Immunomodulation of a hypercoagulable state

Rodriquez, Autoimm Rev 2020
• 5 critically ill/ARDS, also steroids/antivirals—all had improvement [Shen, JAMA 2020]

• 10 severe patients, all improved, 7/10 with (+) viral loads → negative [Duan, PNAS 2020]

• 4 severe/critical (mech vent/ ECMO/ pregnancy), all recovered [Zhang, Chest 2020]
Convalescent Plasma Risks—all rare

- Pathogen transmission
- Antibody-dependent enhancement of infection
- Allergic transfusion reactions
- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
Phase 2/3 of Kevzara (sarilumab) IL-6 receptor blocker

Study compared low and high dose in those with “severe” or “critical” illness

Preliminary phase 2 analysis
  - Negative trends for most outcomes in the severe group
  - Positive trends for all outcomes in critical group

The phase 3 results in those patients with severe illness showed the drug appeared to have no effect.

Ongoing portion of trial will enroll 600 patients with critical illness
Immunomodulators—reversing the Cytokine Storm? Tocilizumab

Soluble Interleukin-6

Interleukin-6

Interleukin-6

Tocilizumab

gp130 signal transduction

June 3, 2020
Tocilizumab (anti-IL6R mab)

1 day post Tocilizumab

Slides from E Tso MD (Hong Kong)
No published data

According to French press, Entire DSMB resigned
• RDV: severe dz only (≤94% RA) or supplemental oxygen
• CQ/HCQ: use only in a clinical trial
  – Against high dose CQ (600 mg BID)
• IVIG (non-SARS-2-CoV): use only in a clinical trial
• IL-6 inhibitors: insufficient data

https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf (5/12/20)
COVID-19 Therapeutics

• In very early phases of understanding

• Numerous trials
  – Patients should be in trials

• Remdesivir, some promise
  – Antivirals need early treatment

• Immunomodulatory therapies
  – Earlier better than later?
The Plenary Abstracts will be broadcast on SAEM’s Facebook Live and YouTube Channel. The anticipated start time is 1:00 - 1:05 PM CDT. We hope you will join us there.