What’s the Buzz Around Various Clinical Trials for COVID-19?

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Disclosures

- I was a co-investigator for ACTT trial
- I do not personally endorse any therapy for COVID-19 other than high quality medical care
What is an adaptive design trial?
Adaptive Covid-19 Treatment Trial (ACTT) (NCT04280705)

• NIH/NIAID sponsored
• Adaptive design
• 1:1 Randomized, Placebo-controlled, double blinded
• Multicenter trial
• ACTT1
  • Remdesivir 200mg d1
  • 100mg d2-10
• Primary outcome: time to recovery
ACTT, Preliminary Findings

• 1063 patients enrolled
• Placebo 15d to recovery, 11d with Remdesivir
  • 31% faster time to recovery ($p=0.001$)
• Placebo 11.6% mortality, 8% with Remdesivir ($p=0.059$)
• Not actively enrolling for the first adaptation
• Trial will adapt based on findings
HCQ + Azithromycin (NCT04358081)

• Novartis sponsored study
• Three arms:
  • HCQ 600mg D1, 200mg tid thereafter
  • HCQ + AZT 500mg d1, 25mg d2-5
  • Placebo
• Multi-center, Randomized, Double-blinded, placebo-control
• Planned 444 patient enrollment
HCQ + Azithromycin

• Primary outcome:
  • % of participants to achieve clinical response

• Enrollment criteria:
  • Adult patient
  • Signs/symptoms less than 7d prior to randomization

• Exclusion Criteria
  • Cytokine storm
  • Concurrent treatment with other SARS-2 therapies
  • CrCl <45
  • EKG abnormalities (historical or present)
  • Pregnancy or women of childbearing age must take contraception

• Not yet recruiting
Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients with Covid-19 (NCT04315298)

- Regeneron Pharmaceuticals sponsored
- Adaptive Phase, Randomized, Double-Blind, Placebo-Controlled Study
- 3 arms:
  - Sarilumab high dose (400mg)
  - Sarilumab low dose (200mg)
  - Placebo
- Phase II/III Clinical Trial
Sarilumab

• Inclusion Criteria:
  • Covid test + w/i 2 weeks
  • Hospitalized with severe disease

• Exclusion Criteria:
  • Low ANC
  • Elevated AST/ALT
  • Treated with IL-6 or Janus Kinas inhibitor

• Primary Outcome:
  • Phase 2: Percent change in CRP in 4 days
  • Phase 3: Time to improvement using –point ordinal scale in patients with IL-6 levels greater than the upper limit of normal
Sarilumab, Preliminary Data

• Phase 2 study: Enrolled 457 patients
  • 28% severe (oxygen requirement)
  • 49% critical (mechanical ventilation, high flow, ICU)
  • 23% MSOD
• Primary Outcome: Drug rapidly lowered CRP at all severity levels
• Exploratory analysis of clinical outcomes from phase 2 focused on severe and critical groups
  • No notable clinical benefit when combining severe + critical v. placebo
## U.S. Kevzara Trial – Phase 2 Efficacy Results

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT (REDUCTION IN C-REACTIVE PROTEIN)</th>
<th>Placebo</th>
<th>Kevzara 200 mg</th>
<th>Kevzara 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change from baseline in CRP (Patients with high baseline IL-6, where data was available)</td>
<td>(n=77)</td>
<td>(n=136)</td>
<td>(n=145)</td>
</tr>
<tr>
<td>-21%</td>
<td>-77%</td>
<td>-79%</td>
<td></td>
</tr>
</tbody>
</table>

## EXPLORATORY CLINICAL ENDPOINTS IN "CRITICAL" GROUP

<table>
<thead>
<tr>
<th>Died or &quot;On a ventilator&quot;</th>
<th>Placebo</th>
<th>Kevzara 200 mg</th>
<th>Kevzara 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>(n=44)</td>
<td>(n=94)</td>
<td>(n=88)</td>
</tr>
<tr>
<td>Died</td>
<td>24 (55%)</td>
<td>43 (46%)</td>
<td>28 (32%)</td>
</tr>
</tbody>
</table>

| Died                      | 12 (27%)| 34 (36%)       | 20 (23%)       |

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<th>On a ventilator</th>
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<td>(n=88)</td>
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<tr>
<td>On a ventilator</td>
<td>12 (27%)</td>
<td>9 (10%)</td>
<td>8 (9%)</td>
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<table>
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<tr>
<th>Clinical improvement (Achieved ≥2 point improvement on 7-point scale)</th>
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<td>Clinical improvement (Achieved ≥2 point improvement on 7-point scale)</td>
<td>18 (41%)</td>
<td>48 (51%)</td>
<td>52 (59%)</td>
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<th>Off oxygenation</th>
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<th>Discharged</th>
<th>Placebo</th>
<th>Kevzara 200 mg</th>
<th>Kevzara 400 mg</th>
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</thead>
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<tr>
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<td>(n=88)</td>
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<td>18 (41%)</td>
<td>37 (39%)</td>
<td>47 (53%)</td>
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</table>
Sarilumab, Preliminary Data

• Phase 2 data suggested negative trends in outcomes in severe group.

• Discontinued severe group
  • Although further analysis from the phase 3 data suggests no differences between severe v. critical

• Discontinued 200mg group
REMAP-COVID (NCT02735707)

• Sub-platform of REMAP-CAP
• Sponsor: MJM Bonten
• Randomized, embedded, multicenter, multifactorial, adaptive trial for community acquired PNA, repurposed for COVID-19
### REMAP-COVID

- Simultaneous evaluation of several domains
- Broad inclusion criteria and then more specific inclusion for each platform

#### D1: Steroids
1. Fixed dependent
2. Shock dependent

#### D2: ABX
1. Ceftriaxone
2. Moxi/Levo
3. Pip/Tazo
4. Ceftaroline
5. Amoxicillin-Clavulanate

#### D3: Immunoglobulin
1. No immunoglobulin
2. Convalescent plasma

#### D4: Antiviral
1. No antiviral
2. Lopinavir-ritonavir
3. HCQ
4. HCQ + Lopinavir/ritonavir

#### D5: Immune Modulation
1. No Immune modulation
2. Interferon-B1a
3. Anakinra
4. Tocilizumab
5. Sarilumab
COVID-19 Vaccines (NCT 04368728)

• Biontech SE/Pfizer
• Randomized, placebo-controlled
• Safety, tolerability, immunogenicity and potential side effects of 4 different vaccine candidates against COVID-19
• 21 arms
  • Low/medium/high dose vaccines
  • 1 or 2 doses
  • 18-55yo, 65-85yo, 18-55yo
  • 3 placebo arms
COVID-19 Vaccines (NCT 04368728)

- Primary Outcomes (10):
  - Local/systemic events
  - Hematology and chemistry changes

- Secondary outcomes:
  - Immunogenicity

- Planned enrollment:
  - 8640 participants
  - Not yet enrolling participants
# Expanded Access to Convalescent Plasma (NCT04338360)

- Led by Mayo Clinic
- Supported by US Government
- More information at uscovidplasma.org
- Study Population: severe or life-threatening manifestations of COVID-19

## Program Participation
May 4, 2020

<table>
<thead>
<tr>
<th>Sites</th>
<th>Physicians</th>
<th>Patients</th>
<th>Infused</th>
</tr>
</thead>
<tbody>
<tr>
<td>2089</td>
<td>4604</td>
<td>10,070</td>
<td>5416</td>
</tr>
</tbody>
</table>
### Expanded Access to Convalescent Plasma

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>ENDPOINTS</th>
<th>JUSTIFICATION FOR ENDPOINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide access to COVID-19 convalescent plasma</td>
<td>Availability of convalescent plasma</td>
<td>Expanded access protocol</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>Serious adverse events</td>
<td>Required as part of expanded access protocol under IND</td>
</tr>
<tr>
<td><strong>Tertiary/Exploratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care utilization</td>
<td>1. Acute care facility length of stay</td>
<td>Evaluation of potential for efficacy</td>
</tr>
<tr>
<td></td>
<td>2. Days spent in intensive care unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Survival to acute care facility discharge</td>
<td></td>
</tr>
</tbody>
</table>