WELCOME to the

Learning Together About COVID-19

Session will start in less than 15 minutes
Current Lit Review:
Remdesivir, Zinc, Vitamin D

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Conflict of Interest Disclosure Statement

No Conflicts of Interest
Objectives

• Discuss current evidence of remdesivir, zinc, and vitamin D for the treatment of COVID-19
Remdesivir Pharmacology

• Broad spectrum modified adenine nucleoside analog
  • Converted to active nucleoside triphosphate metabolite in cells and tissue to inhibit viral RNA polymerases

• Originally developed for treatment of Ebola virus
Remdesivir Evidence

• The evidence for:
  • ACTT
  • SIMPLE

• Inconclusive evidence:
  • Remdesivir in Patients with Severe COVID-19 (Lancet)
ACTT and SIMPLE Trials

• ACTT – placebo controlled, run by NIAID

• SIMPLE trials
  • 2 trials – moderate and severe disease
  • Severe trial – remdesivir 5 days vs. 10 days
  • Moderate trial – remdesivir 5 days vs. 10 days vs. placebo

• SIMPLE trials closing end of May – full publication soon?
ACTT and SIMPLE Trials

• ACTT
  • 31% reduction in recovery time (11 days vs. 15 days, p<0.001)
  • 8% mortality remdesivir vs. 11.6% placebo (p=0.059)

• SIMPLE – Severe
  • No statistical difference observed between 5 days vs. 10 days (OR 0.75, 95% CI 0.51-1.12)
  • 62% of patients enrolled < 10 days from symptom onset discharged at day 14 compared to 49% of patients enrolled > 10 days from onset
ACTT and SIMPLE Trials Criticism

- Awaiting publication of data

- ACTT trial primary outcome modified
  - Current: time to recovery (change in 3 point ordinal scale)
  - Original: percentage of patients reporting severity (7 point ordinal scale)

- Next steps: remdesivir + baricitinib vs remdesivir
Remdesivir in Adults with Severe COVID-19: Lancet 2020

• Randomized, double-blind placebo controlled, multi-center (China)
• SARS-CoV2 positive, onset < 12 days, O2 sat ≤ 94%
• ITT: RDV = 158 patients, placebo = 78

• Primary: time to clinical improvement (6 point scale)
  • 21 days RDV vs. 23 days placebo (HR 1.23, 95% CI 0.87-1.75)

• Secondary:
  • 28 day mortality: 14% RDV vs. 13% placebo (1.1%, 95% CI -8.1 to 10.3)
  • No differences observed time on mechanical ventilation, O2 support
Viral load by quantitative PCR in upper (A) and lower (B) respiratory tract infections.
Lancet 2020: Criticisms

- Statistical power = 58%
- Numerically lower (5 days) difference between RDV and placebo when only comparing patients enrolled ≤ 10 days
- Study is inconclusive
<table>
<thead>
<tr>
<th>Remdesivir Safety</th>
<th>Compassionate Use (n = 163)</th>
<th>SIMPLE (n = 385)</th>
<th>Lancet RDV (n = 155)</th>
<th>Lancet placebo (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>60%</td>
<td>72.5%</td>
<td>66%</td>
<td>64%</td>
</tr>
<tr>
<td>ALT elevations</td>
<td>Elevations reported in 23%, 4 required treatment D/C</td>
<td>Grade 3 – 5% Grade 4 – 2%</td>
<td>2 patients required treatment D/C</td>
<td></td>
</tr>
<tr>
<td>Serious ADEs</td>
<td>N/A</td>
<td>18%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Resp failure or ARDS</td>
<td>4%</td>
<td>N/A</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>N/A</td>
<td>12%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>N/A</td>
<td>N/A</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>4%</td>
<td>N/A</td>
<td>3%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Other events seen: hypoalbuminemia, elevated bilirubin, hypokalemia, anemia, thrombocytopenia,
Zinc Sulfate

• Inhibits RNA dependent RNA polymerase with *in vitro* activity against SARS-CoV
  • Intracellular concentrations are not adequate as monotherapy

• NYU Langhorne – HCQ + Azithro + zinc vs. HCQ + Azithro (not peer-reviewed)
  • Observational period March 2\(^{nd}\) – April 2\(^{nd}\)
    • Zinc added to protocol March 25\(^{th}\) – April 2\(^{nd}\), n = 411
    • Zinc sulfate 220 mg capsule twice daily for 5 days
  • Time to discharge and mortality benefits only seen when ICU patients excluded from analysis
    • Secondary outcomes become contradictory with logistic regression
  • Rapidly changing protocols, disposition, and treatment during trial period
  • Data prior to NEJM/JAMA data that there is no benefit with HCQ + azithro
Vitamin D

- Meltzer – Vitamin D insufficiency associated with greater risk of COVID-19 infection (N = 499, all positive tests at University of Chicago)
  - No difference in infection rate 25OHD < 20 ng/mL (18%) vs 25OHD ≥ 20 ng/mL (12%), p=0.110
  - Higher RR (1.77, p=0.015) of COVID-19 positive test in “likely deficient” compared to “likely sufficient”
  - Similar RR of “Uncertain deficiency” compared to “likely sufficient”

- UK Biobank – (N = 580)
  - No association with vitamin D levels and COVID-19 infection
  - Found associations with sex and ethnicity on infection rates

- Preprint, non-peer reviewed data
- All studies ignoring other factors – socioeconomic, differences in testing strategies, etc.
- No evidence examining the role of vitamin D supplementation
Interpret Pre-Prints with CAUTION

• Title: Vitamin D Insufficiency is Prevalent in Severe COVID-19
• Abstract: “VDI is highly prevalent in severe COVID-19 patients”
• Data: 84.6% of ICU patients had VDI vs. 57.1%. Of patients < 75 years old in the ICU, 100% had VDI
• Retrospective of positive COVID-19 + documented vitamin D
• N = 20... over 1 month in New Orleans...
Interpret Pre-Prints with CAUTION

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Overall (n=20)</th>
<th>ICU (n=13)</th>
<th>Floor (n=7)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.2 ± 16.2</td>
<td>61.5 ± 15.7</td>
<td>72.0 ± 14.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Male</td>
<td>9 (45.0%)</td>
<td>8 (61.5%)</td>
<td>1 (14.3%)</td>
<td>0.07</td>
</tr>
<tr>
<td>African American</td>
<td>15 (75.0%)</td>
<td>11 (84.6%)</td>
<td>4 (57.1%)</td>
<td>0.29</td>
</tr>
<tr>
<td>BMI</td>
<td>31.4 ± 9.3</td>
<td>35.2 ± 7.6</td>
<td>24.5 ± 8.3</td>
<td>0.02</td>
</tr>
</tbody>
</table>

| Comorbidities                 |                |            |             |         |
| Hypertension                  | 15 (75.0%)     | 10 (76.9%) | 5 (71.4%)   | 1.00    |
| Diabetes                      | 7 (35.0%)      | 6 (46.2%)  | 1 (14.3%)   | 0.33    |

| VDI Metrics                   | Reference Range|            |             |         |
| VDI                           | 15 (75.0%)     | 11 (84.6%) | 4 (57.1%)   | 0.29    |
| Serum 25OHD (ng/mL)           | 30.0 - 100.0   | 22.9 ± 12.8| 19.2 ± 10.8 | 0.12    |
| Lowest Platelet Count (10^3/μL)| 130 - 400      | 191.7 ± 74.4| 201.0 ± 79.8| 0.44    |
| Absolute Lymphocyte Count (10^3/μL) | 1.10 - 5.00 | 0.55 ± 0.51| 0.42 ± 0.32 | 0.16    |
Interpreting the data

• Remdesivir
  • Positive results have not undergone peer review
  • Lancet article is inconclusive
  • Interpret with cautious optimism –
    • At best remdesivir helps
    • At worst remdesivir doesn’t harm

• Zinc
  • Monotherapy unlikely helpful
  • Data in favor utilizes treatment deemed ineffective
  • Short term use is low risk

• Vitamin D
  • Association is not causation
  • No data on supplementation
References

- Meltzer DO, Best TJ, Zhang H, et al. Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence. medRxiv 2020.05.08.20095893; doi: https://doi.org/10.1101/2020.05.08.20095893
- Darling AL, Ahmadi KR, Ward KA, et al. Vitamin D status, body mass index, ethnicity and COVID-19: Initial analysis of the first-reported UK Biobank COVID-19 positive cases (n 580) compared with negative controls (n 723). medRxiv 2020.04.29.20084277; doi: https://doi.org/10.1101/2020.04.29.20084277
Thank you!

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