A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of 4/20/20
Remdesivir (GS-5734)

- **Mechanism of Action**: interference with viral RNA polymerase leading to premature termination of viral RNA transcription

- **Investigational agent**
  - Available through Gilead for compassionate use in pediatrics (https://rdvcu.gilead.com/)

- **Pharmacokinetic Highlights**
  - Phosphoramidate prodrug, CYP3A4 substrate
  - Active metabolite half-life of 20.4-25.3 hours
  - Eliminated 63% renally
**Remdesivir Dosing**

**Adult and Children ≥ 40 kg**
- 200 mg/dose IV on day 1 followed by 100 mg/dose IV q24h on days 2-10

**Children < 40 kg**
- 5 mg/kg/dose IV on day 1 followed by 2.5 mg/kg/dose IV q24h on days 2-10
- Dosing recommended for:
  - Post-natal age > 7 days
  - Full-term
  - Serum creatinine < 1 mg/dl
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WHO: “Dosing expected to maintain comparable exposure of adult patients”

Dosing recommended for:
- Post-natal age > 7 days
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- Serum creatinine < 1 mg/dl
COVID-19 Efficacy Data

Adult compassionate use

- 53 patients, 23-84 years old (median age 64 years old)
- 68% of patients showed clinical improvement
- No comparator, need better data to determine efficacy
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No published pediatric data
Safety Data

Adult compassionate use

- 60% reported adverse events
- Most common: increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension
- No comparator arm, confounded by COVID-19

Ebola trial

- One patient developed hypotension from the loading dose
- May have been related to Ebola virus disease

Hydroxychloroquine

• Antimalarial and immunomodulatory agent with therapeutic potential for COVID-19

• Mechanism of Action:
  • Impaired viral receptor glycosylation and intracellular alkalization inhibiting viral replication
  • Reduces cytokine production and inhibits toll-like receptor signaling

• Routine use in pediatrics for rheumatologic conditions

## Hydroxychloroquine Dosing

<table>
<thead>
<tr>
<th>Indication</th>
<th>Pediatric Oral Dose</th>
<th>Max Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatologic</td>
<td>3 – 5 mg/kg/day divided in 1-2 doses</td>
<td>400 mg/day or 7 mg/kg/day</td>
</tr>
<tr>
<td>Condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>13 mg/kg/dose followed by 6.5 mg/kg/dose at 6, 24, 48 hours after first dose</td>
<td>800 mg/dose followed by 400 mg/dose at 6, 24, 48 hours after initial dose</td>
</tr>
<tr>
<td>COVID-19 (Yao X, et al)</td>
<td>6.5 mg/kg/dose BID on day 1 then 3.25 mg/kg/dose BID on days 2-5</td>
<td>400 mg/dose BID on day 1 then 200 mg/dose BID on days 2-5</td>
</tr>
<tr>
<td>COVID-19 (Downes K, et al)</td>
<td>13 mg/kg/dose followed by 6.5 mg/kg/dose at 6, 24, 48 hours after initial dose</td>
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</table>
Hydroxychloroquine PK

Author’s Conclusion: "No known pharmacodynamic target associated with clinical outcomes, no specific recommendations for dosing can be made based simply on simulations"
Hydroxychloroquine PK

200 mg TID for 10 days; 76 kg adult

400 mg BID on day 1 then 200 mg BID on day 2-5; 76 kg adult

400 mg QD for 10 days; 76 kg adult

13 mg/kg once then 6.5 mg/kg at 6, 24, and 48 hours; 40 kg pediatric patient

Authors further state: “Rapidly optimize blood and thus lung tissue concentrations and sustains concentrations with short course therapy”

Author’s Conclusion: “No known pharmacodynamic target associated with clinical outcomes, no specific recommendations for dosing can be made based simply on simulations”

Downes K, et al. OSF pre-print 2020 Mar 31
Safety Data

- Retinopathy (chronic use)
- Rash
- Hypoglycemia
- Gastrointestinal disturbances (nausea, diarrhea, vomiting)
- QTc prolongation
  - Caution use with other QTc prolonging agents

Plaenil (hydroxychloroquine) [prescribing information]. St. Michael, Barbados: Concordia Pharmaceuticals Inc; September 2019.
Safety Data

- Retinopathy (chronic use)
- Rash
- Hypoglycemia
- Gastrointestinal disturbances (nausea, diarrhea, vomiting)

**QTc prolongation**
- Caution use with other QTc prolonging agents

What is a Prolonged QTc in Children?

- Prolonged QTc: > 450 ms
- Severely Prolonged QTc: > 500 ms or > 60 ms from baseline value

Plaquenil (hydroxychloroquine) [prescribing information]. St. Michael, Barbados: Concordia Pharmaceuticals Inc; September 2019.

Too Young for Tablets?

- Package insert recommends to not crush tablets
- Suspension recipes available for patients who cannot take tablets once coating removed
Combination with Azithromycin?

• Azithromycin not routinely indicated in pediatric bacterial community acquired pneumonia unless atypical bacteria suspected

• No pediatric data on combination to support use

• Potential harm from routine combination and use of azithromycin when not otherwise indicated
  • ↑ Risk of QTc prolongation
  • ↑ Antibiotic resistance
Lopinavir/Ritonavir

• **Mechanism of Action:**
  • Lopinavir - HIV protease inhibitor
  • Ritonavir - HIV protease inhibitor, but in combination with lopinavir (LPV/r) is acting as a CYP3A4 inhibitor that increases lopinavir concentrations
  • Inhibits the protease of SARS-CoV-2 inhibiting viral replication

• Routine use in pediatrics for HIV

COVID-19 Efficacy Data

Adult Randomized Trial

• 199 adult-patients with severe COVID-19 randomized to LPV/r or standard of care
• Median age 58 years old

Author’s Conclusion: “In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care”
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No published pediatric data
Safety Data

- **Adverse Events**
  - GI distress (diarrhea, nausea, vomiting)
  - Hepatotoxicity
  - Pancreatitis
  - Diabetes
  - QTc prolongation
  - Lipid elevations and fat redistribution

- **Drug-drug interactions**
  - Major substrate and inhibitor of cytochrome P450 enzymes
  - Must screen for drug-drug interactions

Kaletra (lopinavir and ritonavir) tablets and oral solution [prescribing information]. North Chicago, IL: AbbVie Inc; March 2020.
Safety Data

• **Adverse Events**
  • GI distress (diarrhea, nausea, vomiting)
  • Hepatotoxicity
  • Pancreatitis
  • Diabetes
  • QTc prolongation
  • Lipid elevations and fat redistribution

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University of Liverpool Drug-Interaction Resource
https://www.covid19-druginteractions.org/
Lopinavir/Ritonavir Dosing

• Adults
  • Lopinavir 400 mg/ritonavir 100 mg PO twice daily

• Children
  • Dosed based on lopinavir component with two recommended doses
    1. Lopinavir 300 mg/m$^2$/dose PO (maximum 400 mg/dose) twice daily
    2. Lopinavir 16 mg/kg/dose PO (maximum 400 mg/dose) twice daily
Lopinavir/Ritonavir Dosing

• Adults
  • Lopinavir 400 mg/ritonavir 100 mg PO twice daily

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    1. Lopinavir 300 mg/m²/dose PO (maximum 400 mg/dose) twice daily
    2. Lopinavir 16 mg/kg/dose PO (maximum 400 mg/dose) twice daily

Approximate Lopinavir 300 mg/m² Dose Recommendations

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 – 20 kg</td>
<td>200 mg BID of lopinavir</td>
</tr>
<tr>
<td>21 – 30 kg</td>
<td>300 mg BID of lopinavir</td>
</tr>
<tr>
<td>&gt; 30 kg</td>
<td>400 mg BID of lopinavir</td>
</tr>
</tbody>
</table>
Too Young for Tablets?

• Tablets recommended to not be crushed because of decreased systemic exposure (decrease in AUC by 45 and 47% respectively)

• Commercial solution available for patients that require liquid
  • Solution on shortage in the USA

Tocilizumab

• **Mechanism of Action**: monoclonal antibody against human interleukin type 6 (IL-6) receptor

• Published use of agent limited to adults with COVID-19
  • FDA-approved for cytokine release syndrome and several rheumatologic conditions in those ≥ 2 years old
  • No published data in pediatrics for COVID-19

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n=21 adult patients, mean age 57 years old

**Author Conclusions:**
“Tocilizumab effectively improved clinical symptoms and repressed the deterioration of severe COVID-19 patients”

**Table 2. Laboratory Tests Before and After Tocilizumab**

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Before the tocilizumab</th>
<th>D1</th>
<th>D3</th>
<th>D5</th>
</tr>
</thead>
<tbody>
<tr>
<td>White-cell count, ×10^9/L</td>
<td>3.5–9.5</td>
<td>6.30 ± 2.77</td>
<td>8.05 ± 4.39</td>
<td>6.02 ± 3.05</td>
<td>5.25 ± 2.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4/20, 20.0%)</td>
<td>(8/18, 44.4%)</td>
<td>(9/21, 42.9%)</td>
<td>(2/19, 10.5%)</td>
</tr>
<tr>
<td>Lymphocyte percentage, %</td>
<td>20–50</td>
<td>15.52 ± 8.89</td>
<td>11.78 ± 11.36</td>
<td>16.93 ± 13.59</td>
<td>22.62 ± 13.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(17/20, 85.0%)</td>
<td>(16/18, 88.9%)</td>
<td>(14/21, 66.7%)</td>
<td>(9/19, 47.4%)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>0–5</td>
<td>75.06 ± 66.80</td>
<td>38.13 ± 54.21</td>
<td>10.61 ± 13.79</td>
<td>2.72 ± 3.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20/20, 100%)</td>
<td>(17/18, 94.4%)</td>
<td>(10/20, 50.0%)</td>
<td>(3/19, 15.8%)</td>
</tr>
<tr>
<td>Procalcitonin, ng/ml</td>
<td>0–0.5</td>
<td>0.33 ± 0.78</td>
<td>0.21 ± 0.35</td>
<td>0.09 ± 0.13</td>
<td>0.12 ± 0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2/20, 10.0%)</td>
<td>(2/16, 12.5%)</td>
<td>(1/19, 5.3%)</td>
<td>(1/18, 5.6%)</td>
</tr>
</tbody>
</table>

Data are means ± SD (abnormal no./total no., %).

Tocilizumab

- Published use of agent limited to adults with COVID-19
  - No published data in pediatrics for COVID-19
  - **Increased risk of infection found in rheumatologic patients**
    - (OR 1.3; 95% CI 1.07 to 1.58)

- **COVID-19 Dosing:**
  - 4-8 mg/kg/dose once followed by a one-time repeat dose after 12 hours if lack of clinical improvement (max 800 mg/dose)
  - Should we use higher doses in pediatrics?

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• COVID-19 Dosing:
  • 4-8 mg/kg/dose once followed by a one-time repeat dose after 12 hours if lack of clinical improvement (max 800 mg/dose)
  • Should we use higher doses in pediatrics?

Children < 30 kg: 12 mg/kg/dose?
Neonatal COVID-19

• Investigational Remdesivir
  • Available for compassionate use by Gilead
  • Dosing remains the same if post-natal age > 7 days and neonate is full-term

• Lopinavir-ritonavir
  • May be prescribed for HIV once post-menstrual age of 42 weeks (postnatal age + gestational age)

Personal Communication, Gilead, accessed 4/13/20
• Must scrutinize the evidence closely

• There is currently no proven evidence-based treatment for COVID-19 in pediatrics

• Must consider the benefit-risk ratio of any medication used for COVID-19 in pediatrics