Lopinavir/ritonavir (Kaletra®)

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

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Mechanism of Action – LPV/r

• Antiviral agents for HIV
• Inhibition of HIV-1 protease \(\rightarrow\) formation of immature, noninfectious viral particles

Protease inhibitors

• POTENTIAL INHIBITION of Chymotrypsin-like protease (3CLpro) in SARS-CoV

Lopinavir

• CYP3A4 inhibitor
• DECREASES metabolism = INCREASE serum levels

Ritonavir

• Lopinavir
• Peak: 9.6µg/mL
• Trough: 5.5µg/mL

Monitoring

Dosing

Similar to HIV therapy

400mg /100mg PO twice daily

No renal adjustments

Caution: hepatic impairment

Crushing: may need increased doses

Available Data – *in vitro* data in SARS-CoV-1

Molecular dynamics simulations: LPV/r may inhibit key enzyme

*in vitro* activity for LPV at 4µg/mL after 48h

Cytopathic inhibition seen at 1µg/mL when combined with ritonavir

EC$_{50}$ values for LPV: 17.1-50µM; no activity with ritonavir

Binding site analysis: 1/2 of LPV left outside catalytic site -- poor efficacy

LPV/r may not have effect on replication of SARS-CoV

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Available Data – in vitro data in MERS-CoV

Cytopathic inhibition seen with an EC₅₀ of 8.0µM (SI = 3.1) when combined with ritonavir

- 89% inhibition observed at 12µM

Initial cytopathic effect assay: LPV not effective

- EC₅₀ values for LPV: 11.6µM (SI > 4.3); no significant enhancement with ritonavir

EC₅₀: 50% effective inhibitory concentration; SI: selectivity index

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Observations</th>
</tr>
</thead>
</table>
| Untreated                  | - Increased respiratory rate, reduced movement  
- Loss of appetite, hypothermia  
- Higher mean clinical scores  
- Extensive, multilobar hemorrhagic lung lesions and infiltrates |
| Mycophenolate Mofetil      | - Increased respiratory rate  
- Reduced movement  
- Loss of appetite  
- Hypothermia  
- Higher mean clinical scores  
- Extensive, multilobar hemorrhagic lung lesions and infiltrates  
- Highest mean viral loads in lung |
| LPV/r                      | - No severe sx  
- Less weight reduction  
- Improved mean clinical scores  
- Less pulmonary infiltrates  
- Lowest mean viral loads in lung |
| Interferon-β1b             | - No severe sx  
- Less weight reduction  
- Improved mean clinical scores  
- Less pulmonary infiltrates  
- Lower mean viral loads in lung |
<table>
<thead>
<tr>
<th>Available Data – Animal Data in MERS-CoV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPV</strong></td>
</tr>
<tr>
<td>• EC$_{50}$ of 11.6 µM (SI&gt;4.3)</td>
</tr>
<tr>
<td>• LPV/r EC$_{50}$ of 8.5 µM</td>
</tr>
<tr>
<td>• Minimal effect when used as prophylaxis</td>
</tr>
<tr>
<td><strong>RTV</strong></td>
</tr>
<tr>
<td>• EC$_{50}$ of 24.9 µM (SI&gt;2)</td>
</tr>
<tr>
<td><strong>IFNb</strong></td>
</tr>
<tr>
<td>• EC$_{50}$ of 175 IU/mL (SI&gt;16)</td>
</tr>
<tr>
<td>• Activity not improved when combined w/ LPV/r</td>
</tr>
<tr>
<td>• Minimal effect when used as prophylaxis</td>
</tr>
<tr>
<td><strong>RDV</strong></td>
</tr>
<tr>
<td>• EC$_{50}$ of 0.09 µM (SI&gt;100)</td>
</tr>
<tr>
<td>• Diminished viral replication &amp; disease</td>
</tr>
<tr>
<td>• Reduced acute lung injury</td>
</tr>
<tr>
<td>• Sustained when combined → pointing to monotherapy benefits</td>
</tr>
</tbody>
</table>

RTV: Ritonavir; IFNb: Interferon beta; RDV: Remdisivir
Available Data – Human Data in SARS-CoV-1

Probable SARS

- Ribavirin 2.4g PO LD, 1.2g PO q8h or 8mg/kg IV q8h X 14d + reducing regimen of steroids X 21d
- PLUS Lopinavir/ritonavir 400mg/100mg PO q12h X 14d as INITIAL THERAPY (n=44)
- PLUS Lopinavir/ritonavir 400mg/100mg PO q12h X 14d as RESCUE THERAPY (n=31)

Retrospective, matched cohort

Sex
Age (years)
Co-morbidity
Lactate dehydrogenase

Available Data – Initial vs. Rescue Therapy

**Author Conclusions:**

**Early use** but not rescue use of LPV/r was beneficial in reducing use of pulse corticosteroid therapy, intubation rates, and death. **No significant increases in ADEs.**

*synergism in rescue therapy not established by this study.*

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Table 3. Comparison of outcomes for the group given LPV/r as initial treatment and a matched cohort*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LPV/r as initial treatment, n=44</th>
<th>Matched cohort, n=334</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate (%)</td>
<td>2.3 (0.6-6.8)</td>
<td>15.6 (9.8-22.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Intubation rate (%)</td>
<td>0</td>
<td>11.0 (7.7-15.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Desaturation rate (SaO2&lt;95%) (%)</td>
<td>68.2 (62.3-81.8)</td>
<td>84.5 (74.4-95.2)</td>
<td>NS†</td>
</tr>
<tr>
<td>Proportion requiring pulse</td>
<td>27.3 (11.4-40.0)</td>
<td>55.4 (47.6-63.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>methylprednisolone rescue (%)</td>
<td>1.6 (1.1-2.0)</td>
<td>3.0 (2.8-3.2)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 4. Comparison of outcomes of the group given LPV/r as rescue treatment and a matched cohort*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LPV/r as rescue, n=31</th>
<th>Matched cohort, n=343</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate (%)</td>
<td>12.9 (0-25.3)</td>
<td>14.0 (5.2-26.3)</td>
<td>NS†</td>
</tr>
<tr>
<td>Intubation rate (%)</td>
<td>9.7 (0-22.3)</td>
<td>18.1 (10.0-29.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Desaturation rate (SaO2&lt;95%) (%)</td>
<td>33.5 (80.6-100)</td>
<td>92.1 (75.9-100)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulse methylprednisolone dose (g)</td>
<td>3.8 (3.5-4.2)</td>
<td>3.0 (2.9-3.2)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Available Data – Human Data in SARS**

Open, non-randomized

Probable SARS

Ribavirin 4g PO LD, 1.2g PO q8h or 8mg/kg IV q8h X 14d + reducing regimen of steroids X 21d

Historical controls (n=111)

PLUS Lopinavir/ritonavir 400mg/100mg PO q12h X 14d (n=41)

<table>
<thead>
<tr>
<th>1° Outcome</th>
<th>Historical Controls (n=111)</th>
<th>Treatment group (n=41)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of ARDS or death w/i 21d</td>
<td>32 (28.8%)</td>
<td>1 (2.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death at day 21</td>
<td>7 (6.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>ARDS at day 21</td>
<td>25 (22.5%)</td>
<td>1 (2.4%)</td>
<td></td>
</tr>
</tbody>
</table>
Author Conclusions: When combined with ribavirin, lopinavir appears considerably more effective.

Available Data – Human Data in MERS

Retrospective, matched cohort

PEP in HCWs (n=43)

Ribavirin 2g PO LD, 1.2g PO q8h X 4d, then 600mg PO q8h X 6-8d

PLUS Lopinavir/ritonavir 400mg/100mg PO q12h X 11-13d (n=22)

Non-PEP (n=21)

Author Conclusions:
PEP therapy was associated with a 40% decrease in the risk of infection. There were no severe adverse events during PEP therapy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PEP (n=22)</th>
<th>Non-PEP (n=21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent MERS-CoV infection</td>
<td>0 (0%)</td>
<td>6 (28.6%)</td>
<td>P=0.009</td>
</tr>
<tr>
<td>Safety – ADEs (N/V/D)</td>
<td>21(95.5%)</td>
<td>0(0%)</td>
<td></td>
</tr>
<tr>
<td>MERS-CoV rRTePCR (+)</td>
<td>0%</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

PEP: post-exposure prophylaxis; HCW: healthcare workers

# Available Data — COVID-19 in China

**Open-label, individually randomized**

| SARS-CoV-2 PCR(+) (n=199) | Standard care PLUS LPV/r (400mg/100mg) PO q12h (n=99) X14d | Standard Care (n=100) | **Standard Care**: Supplemental O₂, noninvasive and invasive ventilation, abx, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO) |

<table>
<thead>
<tr>
<th>1° Outcome</th>
<th>LPV/r (n=99)</th>
<th>Standard Care (n=100)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from illness onset to randomization, median days (IQR)</td>
<td>13 (11–17)</td>
<td>13 (10–16)</td>
<td>-</td>
</tr>
<tr>
<td>Time to clinical improvement, median days (IQR)</td>
<td>16.0 (13.0 to 17.0)</td>
<td>16.0 (15.0 to 18.0)</td>
<td>1.31 (0.95 to 1.80)</td>
</tr>
<tr>
<td>ITT 28d mortality, n (%)</td>
<td>19 (19.2)</td>
<td>25 (25.0)</td>
<td>-5.8 (-17.3 to 5.7)</td>
</tr>
<tr>
<td>mITT 28d mortality, n (%)</td>
<td>16 (16.7)</td>
<td>25 (25.0)</td>
<td>-8.3 (-19.6 to 3.0)</td>
</tr>
<tr>
<td>Time from randomization to d/c, median days (IQR)</td>
<td>12 (10 to 16)</td>
<td>14 (11 to 16)</td>
<td>1 (0 to 3)</td>
</tr>
<tr>
<td>Pts w/ clinical improvement at 14d, n (%)</td>
<td>45 (45.5)</td>
<td>30 (30.0)</td>
<td>15.5 (2.2 to 28.8)</td>
</tr>
</tbody>
</table>

Author Conclusions:
LPV/r treatment added to standard txt was not associated w/ clinical improvements or mortality in seriously ill patients with COVID-19 vs. standard care alone. Decrease in viral loads over time did not differ between the two groups.

*high overall mortality, numerical benefits in early txt group and post-hoc groups
Adverse Drug Reactions

- Dermatologic
- Endocrine/Metabolic
- Gastrointestinal
- Respiratory
- Cardiac
- Central Nervous System
- Hepatic
- Hematologic

Drug-Drug

- **CYP3A4 inhibitor**
  - Other HIV and HCV agents
  - Antifungals
  - Amiodarone
  - Apixaban
  - Tacrolimus
  - Agents in psychiatric illness

Drug-Food

- Oral solution
  - High-fat meal can **INCREASE** levels

- Tablets
  - With or without food

# COVID-19?

## Current Evidence
- No current reported study in U.S
- NEJM 3/2020: no benefit in hospitalized adult pts
- Many enrolling in China

## Conflicting Evidence in non-COVID pts
- Improvement in symptoms
- Reduction in viral load

## Treatment Guidelines: China
- LPV/r: recommended as antiviral regimen

## Special Populations
- Pregnancy

## Safety profile - CONCERN
- Diarrhea
- Nausea
- Asthenia
- Anemia
- Hyperbilirubinemia
- Transaminitis

<table>
<thead>
<tr>
<th>Registration number</th>
<th>Registration date</th>
<th>Institution</th>
<th>Title</th>
<th>Enrolment date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChiCTR2000029328</td>
<td>2020/1/21</td>
<td>Wuhan Infectious Diseases Hospital</td>
<td>A randomized, open-label, blind-controlled trial for the efficacy and safety of lopinavir/ritonavir and interferon-α2b in hospitalized patients with novel coronavirus pneumonia (COVID-19)</td>
<td>2020/1/10</td>
</tr>
<tr>
<td>ChiCTR2000029468</td>
<td>2020/2/2</td>
<td>Sichuan People’s Hospital, Sichuan Academy of Medical Sciences</td>
<td>A real-world study for lopinavir/ritonavir (LPV/r) and emtricitabine/tenofovir alafenamide (FTC/TAF) regimen in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)</td>
<td>2020/1</td>
</tr>
<tr>
<td>ChiCTR2000029539</td>
<td>2020/2/3</td>
<td>Tongji Hospital, Huazhong University of Science and Technology</td>
<td>A randomized, open-label study to evaluate the efficacy and safety of lopinavir/ritonavir in patients with mild 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)</td>
<td>2020/2/4</td>
</tr>
<tr>
<td>ChiCTR2000029541</td>
<td>2020/2/3</td>
<td>Zhongnan Hospital of Wuhan University</td>
<td>A randomized, open-label trial comparing darunavir/ritonavir or lopinavir/ritonavir combined with remdesivir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)</td>
<td>2020/2/10</td>
</tr>
<tr>
<td>ChiCTR2000029548</td>
<td>2020/2/4</td>
<td>The First Affiliated Hospital, Zhejiang University School of Medicine</td>
<td>Randomized, open-label, controlled trial evaluating the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients</td>
<td>2020/2/4</td>
</tr>
<tr>
<td>ChiCTR2000029573</td>
<td>2020/2/4</td>
<td>The First Affiliated Hospital of Medical College of Zhejiang University</td>
<td>A multicenter, randomized, open-label, positive-controlled trial for the efficacy and safety of recombinant cytokine gene-derived protein injection combined with abidol, lopinavir/ritonavir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients</td>
<td>2020/2/6</td>
</tr>
<tr>
<td>ChiCTR2000029603</td>
<td>2020/2/6</td>
<td>The First Affiliated Hospital of Zhejiang University School of Medicine</td>
<td>A randomized, open-label, multicenter clinical trial evaluating and comparing the safety and efficiency of ASC09/ritonavir and lopinavir/ritonavir for confirmed cases of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)</td>
<td>2020/2/6</td>
</tr>
<tr>
<td>ChiCTR2000029741</td>
<td>2020/2/11</td>
<td>The Fifth Affiliated Hospital Sun Yat-Sen University</td>
<td>Efficacy of chloroquine and lopinavir/ritonavir in mild/general novel coronavirus (CoV-2019) infections: a prospective, open-label, multicenter randomized controlled clinical study</td>
<td>2020/2/12</td>
</tr>
<tr>
<td>ChiCTR2000029759</td>
<td>2020/2/12</td>
<td>The Second Affiliated Hospital of Chongqing Medical University</td>
<td>A multicenter, randomized, open-label, controlled trial for the efficacy and safety of ASC09/ritonavir compound tablets and lopinavir/ritonavir (Kalstral and Arkidol tablets in the treatment of novel coronavirus pneumonia (COVID-19))</td>
<td>2020/2/15</td>
</tr>
</tbody>
</table>
Summary

- Evidence
- Availability
- Single vs. multi-drug regimens?
  - Interferon
  - Ribavirin
- Safety Profile
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