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 → 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

https://doi.org/10.1097/QAI.0b013e318232b057
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

EC₅₀ 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

Available Data – *in vitro* data in MERS-CoV

Cytopathic inhibition seen with an EC\(_{50}\) of 8.0\(\mu\)M (SI = 3.1) when combined with ritonavir

89% inhibition observed at 12\(\mu\)M

Initial cytopathic effect assay: LPV not effective

EC\(_{50}\) values for LPV: 11.6\(\mu\)M (SI > 4.3); no significant enhancement with ritonavir

EC\(_{50}\): 50% effective inhibitory concentration; SI: selectivity index

### Available Data – Animal Data in MERS-CoV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observations</th>
</tr>
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</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** |

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<table>
<thead>
<tr>
<th>Medication</th>
<th>EC$_{50}$ Value</th>
<th>Activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPV</strong></td>
<td>EC$_{50}$ of 11.6 µM (SI$&gt;$4.3)</td>
<td>LPV/r EC$_{50}$ of 8.5 µM</td>
<td>Minimal effect when used as prophylaxis</td>
</tr>
<tr>
<td><strong>RTV</strong></td>
<td>EC$_{50}$ of 24.9 µM (SI$&gt;$2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IFNb</strong></td>
<td>EC$_{50}$ of 175 IU/mL (SI$&gt;$16)</td>
<td>Activity not improved when combined with LPV/r</td>
<td>Minimal effect when used as prophylaxis</td>
</tr>
<tr>
<td><strong>RDV</strong></td>
<td>EC$_{50}$ of 0.09 µM (SI$&gt;$100)</td>
<td>Diminished viral replication &amp; disease</td>
<td>Reduced acute lung injury</td>
</tr>
</tbody>
</table>

RTV: Ritonavir; IFNb: Interferon beta; RDV: Remdisivir

Available Data – Human Data in SARS-CoV-1

Retrospective, matched cohort

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)

Sex
Age (years)
Co-morbidity
Lactate dehydrogenase

**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 methylprednisolone rescue (%)</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>Mean pulse methylprednisolone dose (g)</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 (6.2-26.3)</td>
<td>14.0 (5.2-26.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Intubation rate (%)</td>
<td>9.7 (4.9-22.6)</td>
<td>18.1 (10.0-29.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Desaturation rate (SaO2&lt;95%) (%)</td>
<td>33.5% (28.6-100%)</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>

*synergism in rescue therapy not established by this study.

**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.**

Available Data – Human Data in SARS

Probable SARS

Ribavirin 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 (n=41)

Historical controls (n=111)

Open, non-randomized

1° Outcome | Historical Controls (n=111) | Treatment group (n=41) | P-value |
--- | --- | --- | --- |
Development of ARDS or death w/i 21d | 32 (28.8%) | 1 (2.4%) | <0.001 |
Death at day 21 | 7 (6.3%) | 0 (0%) |  |
ARDS at day 21 | 25 (22.5%) | 1 (2.4%) |  |

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

<table>
<thead>
<tr>
<th>SARS-CoV-2 PCR(+) (n=199)</th>
<th>Standard care PLUS LPV/r (400mg/100mg) PO q12h X14d (n=99)</th>
<th>Standard Care (n=100)</th>
</tr>
</thead>
</table>

**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
Hepatic
Respiratory
Cardiac
Central Nervous System
Hematologic

Drug Drug & Drug-Food Interactions

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
- Lancet 5/2020: triple therapy

## 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

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Available Data – COVID-19 in China

SARS-CoV-2 PCR(+) (n=127)

Combination Therapy (LPV/r 400mg/100mg PO q12h, ribavirin 400mg q12h PO, and INF-1b SQ) X14d (n=86)

Control (LPV/r 400mg/100mg PO q12h) X 14d (n=40)

Phase 2, multicenter, open-label, randomized

Standard Care: Supplemental O₂, noninvasive and invasive ventilation, abx, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO)

<table>
<thead>
<tr>
<th>Baseline Characteristics (select)</th>
<th>Combination (n = 86)</th>
<th>Control (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>23 (27%)</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (21%)</td>
<td>11 (27%)</td>
</tr>
<tr>
<td>Fever</td>
<td>70 (81%)</td>
<td>32 (78%)</td>
</tr>
<tr>
<td>Cough</td>
<td>45 (52%)</td>
<td>23 (56%)</td>
</tr>
<tr>
<td>Sputum</td>
<td>29 (34%)</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>7 (8%)</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Lymphocytes (1.06–3.61 × 10⁹ per L)</td>
<td>1.0 (0.8–1.5)</td>
<td>1.3 (0.9–1.6)</td>
</tr>
<tr>
<td>LDH (143–280 U/L)</td>
<td>194.0 (159.8–249.0)</td>
<td>167.5 (142.0–200.0)</td>
</tr>
<tr>
<td>CRP</td>
<td>3.0 (2.0–9.2)</td>
<td>3.0 (1.5–7.2)</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>64 (74%)</td>
<td>32 (78%)</td>
</tr>
</tbody>
</table>

NEWS2 – National Early Warning Score, 2nd version

### Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Combination (n = 86)</th>
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<th>p-value</th>
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<tr>
<td>Time to negative RT-PCR in NP swab sample</td>
<td>7 (5-11)</td>
<td>12 (8-15)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Time to NEWS2 of 0 sustained X 24h</td>
<td>4 (3-8)</td>
<td>8 (7-9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to SOFA score of 0 sustained X 24h</td>
<td>3 (1-8)</td>
<td>8 (6.5-9.0)</td>
<td>0.041</td>
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<tr>
<td>Length of hospital stay</td>
<td>9 (7-13)</td>
<td>14.5 (9.3-16.0)</td>
<td>0.016</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Time to negative SARS-CoV-2 RT-PCR in all samples</td>
<td>8 (6-12)</td>
<td>13 (8-15)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0 (0)</td>
<td>1 (2%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Concomitant abx</td>
<td>4 (51%)</td>
<td>25 (61%)</td>
<td>0.33</td>
</tr>
<tr>
<td>O2 therapy</td>
<td>12 (14%)</td>
<td>5 (12%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Non-invasive vent support</td>
<td>3 (3%)</td>
<td>2 (5%)</td>
<td>0.75</td>
</tr>
<tr>
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NEWS2 – National Early Warning Score, 2nd version

Baseline characteristics, SOFA and NEWS2 scores were not indicative of severe illness and may not have warranted admission (if not required). There was no statistically significant difference in 30-d mortality, O2 requirement, and need for ventilatory support.

*ADEs and secondary abx were reported in almost half of pt. population.

Author Conclusions:

Early triple therapy w/ LPV/r, INF-1b, and ribavirin treatment effectively suppressed viral load in all clinical specimens and IL-6. Combination therapy was associated with significantly shorter time to alleviation of symptom and shorter hospital stays. Serious ADEs were similar in both groups, with minimal discontinuation.
Patient randomized to either LPV/r, HCQ, Azithromycin, Convalescent plasma or Tocilizumab
- 4%: invasive mechanical ventilation when entering trial
- 70%: O2 alone
- 26%: no respiratory intervention.

Primary outcome: 28-d mortality
- 22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; p=0.58
- No beneficial effects in 28-d mortality, risk of progression to mechanical ventilation or length of hospital stay.

These interim trial results show that hydroxychloroquine and lopinavir/ritonavir produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care.

*does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalized patients or as pre- or post-exposure prophylaxis for COVID-19
### Summary

- **Evidence** – updated July 2020
- **Availability**
- **Single vs. multi-drug regimens?**
  - Interferon
  - Ribavirin
- **Safety Profile**

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**SIDP**
SOCIETY OF INFECTIOUS DISEASES PHARMACISTS
Lopinavir/ritonavir (Kaletra®)

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

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