SARS-CoV-2 and COVID-19

Treatment: Lopinavir-Ritonavir

David H. Spach, MD
Professor of Medicine
Division of Infectious Diseases
University of Washington

Gretchen Snoeyenbos Newman, MD
Senior Fellow
Division of Infectious Diseases
University of Washington

Last Updated: June 6, 2020
Lopinavir-Ritonavir
Lopinavir-Ritonavir

Lopinavir

Ritonavir
SARS-CoV-2 Main Protease (M\text{\text{\tiny pro}})

- Key enzyme for SARS-CoV-2 replication
- M\text{\text{\tiny pro}} also referred to as 3C-like protease (3CL\text{\text{\tiny pro}})
- Highly similar to SARS-CoV M\text{\text{\tiny pro}} (>96% sequence identity)
- Homodimer structure, each with 3 domains; total \sim 306 aa long
- Initially identified as a potential agent in broad drug-screening surveys following the emergence of SARS-CoV-1 in 2003
- Limited data suggesting possible success in treatment of MERS-CoV and SARS-CoV-1

SARS-CoV-2 Main Protease (SARS-CoV-2M\textsuperscript{pro})

Illustration: David H. Spach, MD
SARS-CoV-2 Main Protease (SARS-CoV-2M\textsuperscript{pro})

Illustration: David H. Spach, MD
SARS-CoV-2 Main Protease (SARS-CoV-2M\textsuperscript{pro})
Lopinavir Binding

Illustration: David H. Spach, MD
SARS-CoV-2 Main Protease (SARS-CoV-2M\textsuperscript{pro})

Rationale for Lopinavir-Ritonavir to Treat SARS-CoV-2

- Fixed-dose combination of boosted protease inhibitor (lopinavir) and pharmacokinetic booster (ritonavir)
- Many years of experience in HIV treatment
- Lopinavir has *in vitro* activity against MERS-CoV and SARS-CoV-1
- Limited data suggested possible success in treatment of MERS-CoV and SARS-CoV-1
- Lopinavir binds to active site of SARS-CoV-2 main protease (M\(^{\text{pro}}\))
- Note: SARS-CoV-2 (M\(^{\text{pro}}\)) not similar to HIV protease
Lopinavir-Ritonavir in Adults with Severe COVID-19

LOTUS Trial (China)

# Lopinavir-Ritonavir in Adults with Severe COVID-19

## LOTUS Trial: Design

### Study Design

<table>
<thead>
<tr>
<th><strong>Background</strong></th>
<th>Randomized, controlled, open-label trial comparing lopinavir-ritonavir to supportive care only in persons with severe COVID-19 disease. Randomization was stratified on respiratory support method at time of enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td>Wuhan, China (January 18-February 3, 2020)</td>
</tr>
</tbody>
</table>
| **Inclusion Criteria** (n = 199)  | - Age ≥18 years  
- Positive SARS-CoV-2 PCR in a respiratory tract sample  
- Pneumonia confirmed by chest imaging  
- O2 sat less than or equal to 94% on room air or PaO2:Fio2 ≤300 mm Hg |
| **Exclusion Criteria** | - Severe liver disease (cirrhosis or liver enzyme >5x ULN)  
- Pregnancy or breastfeeding  
- HIV infection  |
| **Treatment Arms (stratified based on O2 support)** | - Lopinavir-ritonavir: 400-100 mg PO bid x 14 days + Standard care/Control  
- Standard care/Control |
| **Primary Endpoint** | time to clinical improvement |

Lopinavir-Ritonavir in Adults with Severe COVID-19
LOTUS Trial: Design

Randomization

*Symptom onset

Stratified based on O₂ support

- N = 199 adults
- SARS-CoV-2 PCR
- Pneumonia on CXR
- O₂ saturation <94%
  or
  PaO₂:Fio₂ ≤300 mm Hg

Treatment: Days 1-14

Lopinavir-ritonavir + Standard of Care
(n = 99)

Standard of Care
(n = 100)

Outcomes at Day 28

• Primary
  - Time to clinical improvement
• Secondary
  - Mortality at day 28
  - Adverse events

*Median interval time from symptom onset to randomization was 13 days for both groups

## Lopinavir-Ritonavir in Adults with Severe COVID-19

LOTUS China: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Lopinavir-Ritonavir (n = 99)</th>
<th>Control (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median, years)</strong></td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>61.6</td>
<td>59</td>
</tr>
<tr>
<td><strong>Co-existing conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10.1</td>
<td>13</td>
</tr>
<tr>
<td>Cerebrovascular disease, %</td>
<td>5.1</td>
<td>8</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>5.1</td>
<td>1</td>
</tr>
<tr>
<td>Fever, %</td>
<td>89.9</td>
<td>93</td>
</tr>
<tr>
<td>Respiratory rate &gt;24/min, %</td>
<td>21.6</td>
<td>16</td>
</tr>
<tr>
<td>Median WBC count (x 10(^{-9})/liter)</td>
<td>7.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Median serum creatinine (µmol/L)</td>
<td>70.7</td>
<td>67.4</td>
</tr>
<tr>
<td>NEWS2 score at day 1, median (IQR)</td>
<td>5.0 (4.0-6.0)</td>
<td>5.0 (4.0-7.0)</td>
</tr>
<tr>
<td>Days from illness onset to randomization, median (IQR)</td>
<td>13 (11-17)</td>
<td>13 (10-16)</td>
</tr>
</tbody>
</table>

Lopinavir-Ritonavir in Adults with Severe COVID-19
LOTUS Trial: Time to Clinical Improvement (ITT)

Median Time to Clinical Improvement
Lopinavir-ritonavir: 16 days
Control: 16 days

Hazard ratio for clinical improvement: 1.31 [CI, 0.95 -1.85]

Reproduced with permission Massachusetts Medical Society. © 2020 Massachusetts Medical Society.
## Lopinavir-Ritonavir in Adults with Severe COVID-19
### LOTUS Trial: Outcomes

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Lopinavir-Ritonavir</th>
<th>Control</th>
<th>Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (day 28)</td>
<td>19.2%</td>
<td>25.0%</td>
<td>-5.8% [-17.3 -5.7]</td>
</tr>
<tr>
<td>ICU Stay</td>
<td>6 days</td>
<td>11 days</td>
<td>- 5 days [-9 - 0]</td>
</tr>
<tr>
<td>Time to Hospital Discharge</td>
<td>12 days</td>
<td>14 days</td>
<td>1 day [0 - 3]</td>
</tr>
<tr>
<td>Clinical Improvement, day 14</td>
<td>45.5%</td>
<td>30.0%</td>
<td>15.5% [2.2 – 28.8]</td>
</tr>
</tbody>
</table>

Lopinavir-Ritonavir in Adults with Severe COVID-19
LOTUS Trial: Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Lopinavir-Ritonavir</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Clinical Improvement, ITT</td>
<td>Median, 16 days</td>
<td>Median, 16 days</td>
<td>NS</td>
</tr>
<tr>
<td>Time to Clinical Improvement, mITT</td>
<td>Median, 15 days</td>
<td>Median, 16 days</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (day 28)</td>
<td>19.2%</td>
<td>25%</td>
<td>-5.8% [-17.3 -5.7]</td>
</tr>
<tr>
<td>ICU Stay</td>
<td>6 days</td>
<td>11 days</td>
<td>- 5 days [-9 - 0]</td>
</tr>
<tr>
<td>Time to Hospital Discharge</td>
<td>12 days</td>
<td>14 days</td>
<td>1 day [0 - 3]</td>
</tr>
<tr>
<td>Patients with Clinical Improvement at day 14</td>
<td>45.5%</td>
<td>30.0%</td>
<td>15.5% [2.2 – 28.8]</td>
</tr>
</tbody>
</table>

Lopinavir-Ritonavir in Adults with Severe COVID-19
LOTUS Trial: Impact of Treatment on Viral Load

Mean Change from Baseline in SARS-CoV-2 Viral RNA Load on Throat Swabs

Patients with Available Virologic Data
- **Lopinavir-ritonavir**: 59 of 99 patients
- **Control**: 71 of 100 patients

Reproduced with permission Massachusetts Medical Society. © 2020 Massachusetts Medical Society.
Lopinavir-Ritonavir in Adults with Severe COVID-19
LOTUS Trial: Safety data

- ~50% of patients in both groups reported adverse events
- 14% of lopinavir-ritonavir group not able to complete secondary to GI effects
- GI adverse events more common in the lopinavir-ritonavir group
  - 14% in group not able to complete secondary to GI side effects
  - 4 serious gastrointestinal adverse events in the lopinavir-ritonavir group, all determined to be related to the study drug
- Respiratory failure, acute kidney injury, secondary infection, and pneumothorax were more common in the standard care group

Conclusions: “In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.”

Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19 (China)

### Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19: Study Design

<table>
<thead>
<tr>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong>: Randomized, controlled trial of chloroquine for the treatment of SARS-CoV-2 infection in hospitalized patients from Jan 27, 2020 – Feb 15, 2020</td>
</tr>
<tr>
<td><strong>Location</strong>: Zhuhai, China</td>
</tr>
</tbody>
</table>
| **Evaluation**:  
- Viral clearance by RT-PCR  
- Lung imaging by CT chest  
- Length of hospitalization |
| **Inclusion Criteria (n = 22)**  
- Age ≥ 18 years  
- positive for SARS-CoV-2 by RT-PCR |
| **Exclusion Criteria**  
- Pregnancy  
- Contraindication to chloroquine use (history of allergy, retina or hearing dysfunction)  
- History of hematologic, cardiac, renal, or liver disease  
- History of mental illness |
| **Duration of follow up**: 14 days |

Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19: Study Design

Arms and Interventions

Chloroquine
500 mg orally twice daily for 10 days
(n = 10)

or

Lopinavir/ritonavir*
400/100 mg orally twice daily for 10 days
(n = 12)

* At the time of this study, lopinavir-ritonavir was standard of care and used as the control group

Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Chloroquine (n = 10)</th>
<th>Lopinavir/ritonavir (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>41.5 (33.8–50.0)</td>
<td>53.0 (41.8–63.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (70.0)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Coexisting conditions, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (10.0)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (10.0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Severe disease, n (%)</td>
<td>3 (30.0)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Days from onset to treatment*, median (IQR)</td>
<td>2.50 (2.00–3.75)</td>
<td>6.50 (4.75–8.50)</td>
</tr>
</tbody>
</table>

* P-value <0.001

Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19: Results

Comparison of Patients (%) with Negative RT-PCR, by Day

Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19: Results

CT Scan Improvement, by Day

Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19: Results

Clinical Outcomes, by Day

Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19: Results

- There were no statistically significant differences at day 14 in:
  - Rate viral clearance
  - Lung recovery on CT scan
  - Clinical recovery

- Persons treated with chloroquine were more likely to be discharged at day 14

Chloroquine versus Lopinavir-Ritonavir in 22 Patients with COVID-19: Authors’ Conclusions

Conclusions: “Our preliminary results suggest that Chloroquine could be an effective and inexpensive option among many proposed therapies, e.g. Lopinavir/Ritonavir ”.
Published Data – Multicenter, prospective, open-label, randomized, phase 2 trial

Triple Combination of Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19 (Hong Kong)

### Study Design

**Background**: Multicenter, prospective, open-label, randomized, phase 2 trial comparing triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin to lopinavir-ritonavir only in patients hospitalized with COVID-19. Patients were randomized in a 2:1 ratio with no stratification.

**Location**: Hong Kong (February 10-March 20, 2020)

**Inclusion Criteria** (n = 127)
- Age ≥18 years
- National Early Warning Score 2 (NEWS2) ≥1
- Symptom duration ≤14 days upon recruitment
- Laboratory-confirmed SARS-CoV-2 infection by RT-PCR via NP swab

**Exclusion Criteria**:
- Second- and third-degree heart block
- Severe depression
- Pregnancy

**Treatment Arms**
- Combination Arm: Lopinavir-ritonavir + ribavirin + Interferon beta-1b + standard of care
- Control Arm: Lopinavir-ritonavir 400-100 mg PO BID + standard of care

---

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Study Design

<table>
<thead>
<tr>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
</tr>
<tr>
<td>- Time to achieve negative RT-PCR for SARS-CoV-2 in NP swab sample</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
</tr>
<tr>
<td>- Time to NEWS2 of 0</td>
</tr>
<tr>
<td>- Daily NEWS2 and sequential organ failure assessment (SOFA) score</td>
</tr>
<tr>
<td>- Length of hospitalization</td>
</tr>
<tr>
<td>- 30-day mortality</td>
</tr>
</tbody>
</table>

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Study Design

Arms and Interventions

**Lopinavir-ritonavir 400-100 mg orally + ribavirin 400 mg orally every 12 hours, and interferon beta-1b 1 mL subcutaneously on alternate days for 14 days*** (n = 86)

or

**Lopinavir-ritonavir 400-100 mg orally every twelve hours for 14 days** (n = 41)

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>LPV-RTV, IFN-beta 1b, RBV* (n = 86)</th>
<th>LPV-RTV Only (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>51.0 (31.0–61.3)</td>
<td>52.0 (33.5–62.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>45 (52%)</td>
<td>23 (56%)</td>
</tr>
<tr>
<td>Coexisting conditions, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (27%)</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (13%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>NEWS2 Score, n (IQR)</td>
<td>2 (1-2)</td>
<td>2 (2-2)</td>
</tr>
<tr>
<td>SOFA Score, n (IQR)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Days from onset to treatment, median (IQR)</td>
<td>5 (4–7)</td>
<td>4 (3–8)</td>
</tr>
</tbody>
</table>

*Abbreviations: LPV = Lopinavir, RTV = ritonavir, IFN = interferon, RBV = ribavirin

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Results

Comparison Between Combination and Control Groups: Days to Achieve Endpoints

- Negative RT-PCR: 7 vs. 4
- NEWS2 Score of 0: 8 vs. 3
- SOFA score of 0: 8 vs. 9
- Hospital Duration: 14.5 vs. 9

*Abbreviations: LPV = Lopinavir, RTV = ritonavir, IFN = interferon, RBV = ribavirin

# Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LPV-RTV, IFN-beta 1b, RBV* (n = 86)</th>
<th>LPV-RPV Only (n = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint, days (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Time to negative RT-PCR in NP Swab</td>
<td>7 (5–11)</td>
<td>12 (8–15)</td>
<td>0.0010</td>
</tr>
<tr>
<td><strong>Secondary Endpoints, days (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Time to NEWS2 Score of 0</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</td>
<td>3.0 (1.0–8.0)</td>
<td>8.0 (6.5–9.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>- Duration of hospital days</td>
<td>9·0 (7.0–13.0)</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>
</tbody>
</table>

*Abbreviations: LPV = Lopinavir, RTV = ritonavir, IFN = interferon, RBV = ribavirin

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Results

- **Primary Endpoint: Median time to SARS-CoV-2 negative NP swab**
  - Significantly shorter in combination group than control group (HR 4.37 [95% CI 1.86-10.24], p=0.001)
  - No statistically significant difference between treatment groups in patients who started treatment ≥7 days after symptom onset

- **Secondary Endpoints**
  - Statistically significant outcomes in combination group for:
    - Time to achieve NEWS2 and SOFA score of 0
    - Median length of hospital stay

- **Time to achieve negative viral load across all samples collected**
  - No statistically significant differences between treatment groups in patients who started treatment ≥7 days after symptom onset (except NEWS2 score on Day 5)

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Safety Data

- Adverse events were reported in 41 of 86 (48%) patients in combination group and 29 of 41 (49%) in control group
- Side effects were generally mild and self-limiting
- No serious adverse events were reported in combination group
- 1 patient in the control group had a serious adverse event requiring discontinuation of treatment

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Authors’ Conclusions

Interpretation: “Early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19. Future clinical study of a double antiviral therapy with interferon beta-1b as a backbone is warranted”.