Outpatient Oral Therapies for COVID-19

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Disclosures

• Research support:
  – Ansun, F2G, Zeteo

• Advisory Board/Consulting/Data Safety Monitoring Board
  – Adagio, Adamis, Celltrion, Immunome, Intermountain Health,
Objectives

• Be aware of the major outpatient therapeutic options for COVID-19
• Understand the role of antiviral and immunomodulatory approaches to outpatient treatment
• Understand important drug interactions with oral COVI-19 therapies
Oral therapies I will Review

- Paxlovid (nirmatrelvir/ritonavir)
- Molnupiravir
- Fluvoxamine
GARTNER HYPE CYCLE

Expectedations

Innovation Trigger
Trough of Disillusionment
Peak of Inflated Expectations
Slope of Enlightenment
Plateau of Productivity

Time
A 70-year-old man that you have been following for many years calls your office. He has sore throat, cough, headache, fevers and myalgias. He is not short of breath.

His medical history includes hypertension, diabetes, hyperlipidemia and depression.

His grandson has COVID-19 and your patient’s home antigen test is now positive for SARS-CoV-2.
Virus, antibody, infections and illness
Clinical Progression

Schematic of Clinical Course of Severe COVID-19

JHMI Clinical Recommendations for Available Pharmacologic Therapies for COVID-19
https://www.hopkinsguides.com/hopkins/ub?cmd=repview&type=479-1155&name=14_538747_PDF
Clinical Course:

• Illness severity (pre vaccine and pre-treatment era)
  
  o Mild to moderate (mild symptoms to mild pneumonia): 81%
  o Severe (dyspnea, hypoxia, or > 50% lung involvement on imaging): 14%
  o Critical (respiratory failure, shock, multiorgan dysfunction): 5%

Hospitalization rates vaccination era

  o Vaccinated person with breakthrough COVID: ~2%
  o Unvaccinated person with COVID: ~10%
  o Unvaccinated person > 60 years of age: ~18%

## CDC: Risk Factors for Severe Illness

<table>
<thead>
<tr>
<th>Meta-analysis, systematic review</th>
<th>Cohort, case-control, cross-sectional studies</th>
<th>Case series, case reports</th>
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<tbody>
<tr>
<td>Cancer</td>
<td>Children with certain underlying conditions</td>
<td>Cystic fibrosis</td>
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<tr>
<td>Cerebrovascular disease</td>
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<td>Thalassemia</td>
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<td>CKD</td>
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<td>COPD</td>
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<td>Serious heart conditions (HF, CAD, cardiomyopathies)</td>
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<tr>
<td>Smoking (current/former)</td>
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<td>Obesity (BMI ≥ 30)</td>
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<td>Pregnancy/recent pregnancy</td>
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<td>T1DM</td>
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<td>T2DM</td>
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</table>

Mixed evidence

Risk of Death by Age and Chronic Conditions

# Risk for COVID-19 Infection, Hospitalization, and Death By Race/Ethnicity

<table>
<thead>
<tr>
<th>Rate ratios compared to White, Non-Hispanic persons</th>
<th>American Indian or Alaska Native, Non-Hispanic persons</th>
<th>Asian, Non-Hispanic persons</th>
<th>Black or African American, Non-Hispanic persons</th>
<th>Hispanic or Latino persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>1.7x</td>
<td>0.7x</td>
<td>1.1x</td>
<td>1.9x</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>3.5x</td>
<td>1.0x</td>
<td>2.8x</td>
<td>2.8x</td>
</tr>
<tr>
<td>Death</td>
<td>2.4x</td>
<td>1.0x</td>
<td>2.0x</td>
<td>2.3x</td>
</tr>
</tbody>
</table>

Right Drug, Right Time, Right Patient

• Proper patient selection is important (Goldilocks effect)
  – Some people will get better without treatment
  – Some people will benefit from treatment: \textit{timing is critical}
  – Some will not get better with treatment
What is true today may not be so in a few months

- Respiratory viruses are often mutating
- In the community: emergence of variants means that therapies effective in one region may not be effective in others.
- Escape mutants: in certain patients (e.g., immunocompromised) mutants may develop as a consequence of therapy
Nirmatrelvir renders the SARS-CoV-2 main protease (Mpro) incapable of processing polyprotein precursors thereby preventing viral replication.

Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.
Clinical Data

- RCT of 2,246 outpatient adults with mild to moderate COVID who were at risk for progression and within 5 days of onset of symptoms.
- Non vaccinated and no history of COVID-19
- 1:1 drug vs placebo

<table>
<thead>
<tr>
<th></th>
<th>PAXLOVID (N=1,039)</th>
<th>Placebo (N=1,046)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 related hospitalization or death from any cause through Day 28 n (%)</td>
<td>8 (0.8%)</td>
<td>66 (6.3%)</td>
</tr>
<tr>
<td>Reduction relative to placebo [95% CI], %</td>
<td>-5.62 (-7.21, -4.03)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality through Day 28, %</td>
<td>0</td>
<td>12 (1.1%)</td>
</tr>
</tbody>
</table>
Subgroups

- Overall (mITT)
- Symptom onset duration: <= 3 days
- Symptom onset duration: > 3 days
- Age: <= 60 years
- Age: > 60 years
- Gender: Male
- Gender: Female
- BMI: < 30 kg/m**2
- BMI: >= 30 kg/m**2
- Diabetes mellitus = Yes
- Diabetes mellitus = No
- Baseline SARS-CoV-2 serology status: Negative
- Baseline SARS-CoV-2 serology status: Positive
- Received/expected to receive COVID-19 mAbs treatment: Yes
- Received/expected to receive COVID-19 mAbs treatment: No
Authorization

- Mild-to-moderate COVID-19
- Adults and kids 12 years of age and older weighing at least 40 kg
- Positive results of direct viral testing
- High risk for progression to severe COVID-19
- Start within 5 days of symptom onset
Drug Interactions with Paxlovid

STATIN  NIRMA

CYP3A

RITONAVIR

inactive metabolite

Protease inhibitor

Booster
Contraindicated Drugs (part 1)

- Drug that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions
  - Alpha$_1$-adrenoreceptor antagonist: alfuzosin
  - Analgesics: pethidine, piroxicam, propoxyphene
  - Antianginal: ranolazine
  - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
  - Anti-gout: colchicine
  - Antipsychotics: lurasidone, pimozide, clozapine
  - Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
  - HMG-CoA reductase inhibitors: lovastatin, simvastatin
  - PDE5 inhibitor: sildenafil when used for pulmonary arterial hypertension (PAH)
  - Sedative/hypnotics: triazolam, oral midazolam
Contraindication Drugs (part 2)

Strong CYP3A Inducers

- Contraindicated with drugs that are potent CYP3A inducers as nirmatrelvir or ritonavir plasma concentrations may be significantly reduced
  - Anticancer drugs: apalutamide
  - Anticonvulsant: carbamazepine, phenobarbital, phenytoin
  - Antimycobacterials: rifampin
  - Herbal products: St. John’s Wort (*hypericum perforatum*)
Dosing

- Normal Renal function
  - 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) BID x 5 days
- Moderate renal impairment (eGFR 30-59)
  - 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) BID x 5 days
- Severe renal impairment (eGFR <30)
  - Not recommended at this time

<table>
<thead>
<tr>
<th>Cmax (µg/mL)</th>
<th>Normal Renal Function (n=8)</th>
<th>Mild Renal Impairment (n=8)</th>
<th>Moderate Renal Impairment (n=8)</th>
<th>Severe Renal Impairment (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.60 (31)</td>
<td>2.08 (29)</td>
<td>2.21 (17)</td>
<td>2.37 (38)</td>
<td></td>
</tr>
<tr>
<td>14.46 (20)</td>
<td>17.91 (30)</td>
<td>27.11 (27)</td>
<td>44.04 (33)</td>
<td></td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2.0 (1.0 - 4.0)</td>
<td>2.0 (1.0 - 3.0)</td>
<td>2.50 (1.0 - 6.0)</td>
<td>3.0 (1.0 - 6.1)</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>7.73 ± 1.82</td>
<td>6.60 ± 1.53</td>
<td>9.95 ± 3.42</td>
<td>13.37 ± 3.32</td>
</tr>
</tbody>
</table>

February 17, 2022
Molnupiravir

Incorporation into viral RNA

Errors in viral genome

Inhibition of replication

NHC-TP

NHC
Clinical data

- RCT of 1,433 outpatient adults with mild-to-moderate COVID who are at risk for progression and within 5 days of onset of symptoms
- Non vaccinated and no history of COVID-19
- 1:1 drug vs placebo

<table>
<thead>
<tr>
<th></th>
<th>Molnupiravir (N=709)</th>
<th>Placebo (N=699)</th>
<th>Adjusted Risk Difference % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospitalization ≥24 hours for acute care or death through Day 29</td>
<td>48 (6.8%)</td>
<td>68 (9.7%)</td>
<td>-3.0% (-5.9%, -0.1%)</td>
</tr>
<tr>
<td>All-cause mortality through Day 29</td>
<td>1 (0.1%)</td>
<td>9 (1.3%)</td>
<td></td>
</tr>
</tbody>
</table>
Subgroups

Time from Symptom Onset to Randomization
- ≤ 3 days
- > 3 days

Age
- ≤ 60 years
- > 60 years

Sex
- Male
- Female

Obesity (BMI ≥ 30)
- Yes
- No

Diabetes Mellitus
- Yes
- No

Baseline COVID Severity
- Mild
- Moderate

Most Common Baseline Clades
- 20J (Gamma)
- 21A, 21I, 21J (Delta)
- 21H (Mu)
- Other

Baseline Antibody Status
- Positive
- Negative
Authorization

- Mild-to-moderate COVID-19
- Adults 18 years and old
- Positive results of direct viral testing
- High risk for progression to severe COVID-19 and for whom other treatment options are not accessible or clinically appropriate.
- Start within 5 days of symptom onset
WARNINGS

- Embryo-Fetal Toxicity: Not recommended during pregnancy.
- Bone and Cartilage Toxicity: Not authorized for kids because it may affect bone and cartilage growth.
- Molnupiravir and NHC are mutagenic in vitro. Equivical results in a pig model.
Dosing

- 800 mg (four 200 mg capsules) PO BID x 5 days
- No change needed for renal function
Fluvoxamine for COVID-19: Potential Mechanisms

– Immune modulation
  • Sigma-1 receptor activation, leading to inositol-requiring enzyme 1α-driven (IRE1) inflammation ↓
  • platelet aggregation ↓
  • mast cell degranulation ↓
  • melatonin level ↑ (Melatonin may reduce inflammation through inhibition of the NLRP3 pathway)

– Antiviral effect
  • Interference with viral entry and endolysosomal viral trafficking
Fluvoxamine vs Placebo for Outpatients With Symptomatic COVID-19

• Lenze et al, JAMA 2020
  – RCT (n=152); outpatient
  – Fluvoxamine 50 mg x 1 dose, then 100 mg BID x 2-3 days then 100 mg TID as feasible (only 50% got up to that dose) x 15 days
  – Clinical deterioration: 0/80 FLX patients vs 6/72 (8.3%) placebo (P = .009)
Primary endpoint: clinical deterioration (dyspnea PLUS hypoxia [O2<92%])

Fluvoxamine group: 0% (0/80) deteriorated

Placebo group: 8.3% (6/72) deteriorated.

Lenze et al., JAMA 2020
Prospective Cohort of Fluvoxamine for Early Treatment of COVID-19

- Seftel et al, OFID 2021
  - Prospective self selected cohort in the setting of a mass outbreak (n=65 FLX, 48 usual care)
  - Fluvoxamine 50 mg twice daily
  - Hospitalization 0/65 FLX vs. 6/48 (12.5%) for observation alone
  - Residual symptoms at 14 days 0/65 FLX vs. 29/48 (60%) with observation.
Observational Cohort

Prospective cohort of fluvoxamine for early treatment of COVID-19

- Mass Occupational Outbreak in California
  - N = 65
  - 113 non-hospitalized persons
    + Detected by rapid Ag tests
    + Confirmed by PCR
    - All offered Fluvoxamine as an optional therapy
  - N = 48
  - Fluvoxamine 50mg 2x daily for 14 days
  - Hospitalization: 0% (0/65)
  - Symptoms at 14 days: 0% (0/65)
  - Observation Alone
    - Hospitalization: 12.5% (6/48)
    - Symptoms at 14 days: 60% (29/48)

Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of COVID-19. Open Forum Infectious Diseases; 2021
Doi: 10.1093/ofid/ofab050
Fluvoxamine: Together Trial

- N = 1497 Together RCT (Brazil, multicenter)
- Interim analysis RCT: 10-day BID course; within 7 days of symptom onset
- Reduced need for hospitalization or ED visit > 6 hr
  - Fluvoxamine 11% (79/741) vs. 16% (119/756) placebo; one death vs 12 in placebo
  - Relative Risk = 0.68; 95% CI: 0.52 - 0.88
- No differences
  - Viral clearance day 7
    - OR = 0.67; 95% CI: 0.42 – 0.96
  - Mortality (outpatient trial)
    - OR = 0.69; 95% CI: 0.36 – 1.32
  - Length of hospitalization
    - Mean ∆ = 1.2 days; 95% CI: 0.99 - 1.53
  - Ventilator days
    - Mean ∆ = 1.03 days; 95% CI: 0.64 - 1.67

Reis G et al. Lancet Global Health 2021
Questions?

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