COVID-19

INVESTIGATIONAL TREATMENTS FROM A PHARMACIST PERSPECTIVE

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- The following presentation considers information as of 4/20/2020 and will be use to discuss experimental and potential therapies for COVID-19

- All decisions for patient care are the responsibility of local provider in coordination with the patient or patient relatives.
There are no US Food and Drug Administration (FDA)-approved drugs specifically for the treatment of patients with COVID-19.
3.28.2020 - Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease

- Adult and adolescent patients who weigh 50 kg or more and are hospitalized with COVID-19, for whom a clinical trial is not available, or participation is not feasible
SARS-CoV-2 Cycle

POTENTIAL TARGET FOR ANTIVIRALS
REMDESIVIR (GS-5734™)

MOA: Adenosine nucleotide analogue, incorporates into viral RNA. Inhibits RNA synthesis

- Developed for Ebola
  - In vitro activity against SARS-CoV and MERS-CoV as prophylactic and therapeutic agent
  - Potent inhibition of SARS-CoV-2 (in vitro)
  - Clinical experience is limited
- Dosing: 200mg IV once, followed by 100mg IV once daily for 10 days
  - Not recommended in GFR < 30ml/min

Not currently FDA-approved and must be obtained via compassionate use, expanded access, or enrollment in a clinical trial

Total of 10 Clinical trials in clinicaltrials.gov

- Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™)
  - Mild/moderate Pneumonia
  - Severe Pneumonia
  - ARDS

- DisCoVeRy Trial (5 arm trial)
  - Multicenter RCT to evaluate safety and efficacy of treatment for COVID-19 in hospitalized patients

Standard of care (SoC) vs SoC/RDV vs SoC/LPV/r vs SoC/LPV/r + Interferon vs SoC/HCQ
**Promising results**

- **Recent cohort analysis of 53 patients hospitalized with severe complications**
  - 34 receiving mechanical ventilation
  - 4 patients on ECMO
  - Patients received 200mg on day one, followed by 100mg daily x 10 days

- **Results (follow-up 18 days post dose)**
  - 68% had improvement in oxygen support
  - 57% of patients in mechanical ventilation were extubated
  - 75% of the patients on ECMO stop receiving this support and alive
  - 47% of all patients were discharge home

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*REMDESIVIR (GS-5734™, RDV)*

**POTENTIAL ANTIVIRAL**

**Compassionate Use Of Remdesivir For Patients with Severe Covid-19:**

*Nejm*

Jonathan Grein-J. Grein-D. Sutton-N. Doremalen-Sinai Medical Center -

Clinical improvement was observed to be less frequent in patients on invasive ventilation and in elderly patients (>70yo vs <50yo)

Compassionate Use Of Remdesivir For Patients with Severe Covid-19: Nejm
Chloroquine
Hydroxychloroquine

POTENTIAL TARGET FOR ANTIVIRALS

Antiviral activity

MOA: Interferes with endosome-mediated viral entry of enveloped viruses

- Interferes with glycosylation of cellular receptors
- Increases endosomal pH required for viral fusion

Anti-inflammatory properties

- Stopping production of TNF, IL-6, IL-1
  - May control cytokine storm that occurs late phase in critically ill SARS-CoV-2

In vitro activity against MERS/SARS

No high-quality evidence exist for efficacy

Then why Hydroxychloroquine instead?

- Hydroxyl analog of chloroquine with similar MOA but may have more favorable dose related toxicity profile
- Both drugs have in-vitro activity against SARS-CoV, SARS-CoV-2, and other coronaviruses, with hydroxychloroquine having relatively higher potency against SARS-CoV-2

Hydroxychloroquine: Clinical experience
Small pilot study conducted in China

- Total of 30 patients
  - Confirmed COVID-19 patients
  - Tx Naïve
  - Randomized 1:1
    - Hydroxychloroquine (HCQ)
    - Standard of Care (SoC)
  - Both groups also received Interferon, LPV/r or umifenovir

- **Primary Outcome:** Conversion to a negative PCR in nasopharyngeal swab at day 7
  - Conversion to a negative PCR in nasopharyngeal swab at day 7

- **Results:**
  - No statistical significant differences in time to viral clearance at day 7
  - COVID-19 PCR swabs was negative in 13/15 (86.7%) of the patients treated with HCLQ and 14/15 (93.3%) cases in the control group
  - No difference in clinical outcomes
  - Duration of fever, changes in lung imaging

- **Conclusions:** Larger sample size study are needed to investigate the effects of HCLQ in the treatment of COVID-19

Hydroxychloroquine: Clinical experience

Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial

Total of 62 patients
- Confirmed COVID-19 patients with pneumonia
- Mild pneumonia (>93% SaO2)
- Randomized 1:1
  - Hydroxychloroquine (HCQ)
  - Standard of Care (SoC)
    - O2, immunoglobulin, antibacterial tx w/ or w/o corticosteroids

Primary Outcome: No viral load measure
- Measurement of time to clinical recovery
  - Normalization of fever, cough and maintained for > 72hrs, changes of chest CT

Results:
- Compared to control patients, the HCQ treated patients had 1 day shorter mean duration of fever (2.2 days vs 3.2 days) and cough (2 days vs 3.1 days)
- Larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31)
- Adverse effects (1 headache, 1 rash) occurred among 2 (6.4%) of patients in the HCQ-treated group.

Limitations
- Sample size is small
- Standard treatment was complex and not well defined
- No comorbidities documented
- No blinding

Hydroxychloroquine: Clinical experience

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Total of 36 patients
- Confirmed COVID-19 patients with pneumonia
- Tx Naïve
- 36 patients (not randomized)
  - Hydroxychloroquine (HCQ)
  - Untreated
  - Azithromycin

Primary Outcome:
- Negative PCR of nasopharyngeal samples at day 6

Hydroxychloroquine
POTENTIAL TARGET FOR ANTIVIRALS

Hydroxychloroquine

POTENTIAL TARGET FOR ANTIVIRALS

8/14 (57%)

6/6 (100%)

LIMITATIONS

- Study was small non randomized
- Was not design to compare HCLQ with HCLQ PLUS azithromycin
  - Those patients received azithromycin to prevent bacterial infections based on clinical judgement
- Severity of the patients was not clear
  - there were asymptomatic patients in the trial
  - There were no data on disease progression

Hydroxychloroquine: Clinical experience

Hydroxychloroquine in patients with COVID-19: an open label, randomized controlled trial

Total of 150 patients
- Confirmed COVID-19 patients with pneumonia
- Tx Naïve
- Stratified by disease severity
  - Hydroxychloroquine (HCQ)
    - LD: 1200mg/d x 3 days
    - 800mg/d x 2wks moderate infx
    - 800mg/d x 3 wks severe infx
  - Standard of care

Primary Outcome:
- 28day-negative conversion rate SARS-CoV-2

Secondary measures
- Negative conversion rate at day 4, 7, 10, 14, 21
- Improvement of clinical symptoms within 28 days
- Normalization of C-reactive protein

Results:
- 28day-negative conversion rate SARS-CoV-2 was similar in both groups
- Negative conversion rate at day 4, 7, 10, 14, 21 was comparable in both groups
- There was a more rapid alleviation of the symptoms observed in the HCQ group
- More rapid normalization of C-reactive protein in HCQ group

medRxiv 2020.04.10.20060558; doi: https://doi.org/10.1101/2020.04.10.20060558
CONCERNS FOR ADDITIVE CARDIOTOXICITY

Drug induced QT prolongation has served as a surrogate indicator for increased risk of fatal arrhythmias

- Both drugs can cause QT prolongation
- Electrocardiography is recommended at baseline and following initiation

<table>
<thead>
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<th>Risk factors for drug-associated QTc Prolongation</th>
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<td>Heart Failure or acute MI</td>
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<td>≥ 2 QT prolonging medications</td>
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Hydroxychloroquine / Azithromycin

CONCERNS FOR ADDITIVE CARDIOTOXICITY

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Risk factors for drug-associated QTc Prolongation

- Age ≥ 68 years
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- Loop diuretics
- Serum K+ ≤ 3.5 mEq/L
- QTc ≥ 450 ms

Hydroxychloroquine plus Azithromycin

Recommendation:
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of hydroxychloroquine plus azithromycin for the treatment of COVID-19, except in the context of a clinical trial (AIII).

Rationale for Recommendation:
Chloroquine and hydroxychloroquine for COVID-19 have been used in small randomized trials and in some case series with conflicting study reports (as described above). The combination of hydroxychloroquine and azithromycin was associated with QTc prolongation in patients with COVID-19.
Lopinavir/ritonavir (LPV/r)

FDA approved for the treatment of HIV

- In vitro activity against other novel coronaviruses via inhibition of 3-chymotrypsin-like protease
  - No in vitro information on SARS-CoV-2
  - Clinical studies with SARS were associated with reduced mortality
  - No difference in clinical improvement
  - No difference in viral clearance
  - No difference in 28 day mortality rates

Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.
**Recommendation 1.** Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap)

**Recommendation 2.** Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)

**Recommendation 3.** Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)
Adjunctive Therapies

FOR POTENTIAL MANAGEMENT OF COVID-19

- USE OF CORTICOSTEROIDS
- Immunomodulatory agents
TOCILIZUMAB-ACTEMRA

FDA approved for the treatment rheumatoid arthritis and cytokine release syndrome (severe or life-threatening)

- Monoclonal antibody against key inflammatory cytokine
- Use as adjunctive therapy during hyperinflammatory phase of COVID-19 infection
  - Rationale for use: to prevent further damage of the lung and other organs caused by an amplified immune response
  - Theoretically antibodies against IL-6 reduce the inflammatory process and improve clinical outcomes
  - Should be use in the setting of clinical trial
    - Description of drug use criteria is highly recommended

- Level of evidence is poor
  - Single report of 21 patients with severe COVID-19 infection showed clinical improvement

**Recommendation 6.** Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)
In-vitro studies ≠ in-vivo

Variability between human subjects

✓ Absorption
✓ Distribution
✓ Metabolism
✓ Excretion
We encourage enrollment of patients in clinical research protocols, whenever possible

- All clinical use that occurs outside of a research setting should incorporate anticipated benefits balanced against risks.
THANK YOU