Treatment Options for COVID-19

June 3, 2020   Ellie Sukerman, MD
Objectives

• Review pharmacologic therapies available and/or under investigation for COVID-19

• How to access select medications

• Guidance on concomitant medications
Quick Virology Overview

Repurposed and Experimental Agents

Image: https://www.nature.com/articles/d41591-020-00019-9
Therapy by Disease Severity

- Mild COVID-19 -> symptomatic treatment
- Moderate and severe COVID-19 -> consider therapy

NIH Treatment Guidelines Summary

- Do not recommend the use of any agents for pre- or post-exposure prophylaxis outside a clinical trial
- No specific treatment recommended for persons with suspected or confirmed asymptomatic or pre-symptomatic infection
- Currently, no drug has been proven to be safe and effective for treating COVID19. Insufficient data to recommend either for or against the use of any antiviral or immunomodulatory agent

What’s old is new again...

- Hydroxychloroquine (HCQ), Chloroquine (CQ)
- Lopinavir/ritonavir (LPV/r)
- Ribavirin
- Umifenovir (Arbidol)
- Nitazoxanide
- Ivermectin
HCQ

- *In vitro* activity against SARS-CoV-2
- Relatively well tolerated but can cause serious adverse effects (e.g., QTc prolongation, ventricular arrhythmia, retinopathy, hypoglycemia)

- Initial publications reported positive results but data limited by study design, study design flaws, small numbers

HCQ +/- azithromycin

• Gautret, et al. – open-label, non-randomized trial
HCQ + azithromycin

- Gautret, et al. - pilot observational study
  - Uncontrolled, non-comparative, observational study in cohort of 80 inpatients treated with HCQ and azithromycin x min. 3d

- Million, et al. – retrospective analysis
  - 1061 inpatients treated with same regimen for min. 3d

- Both studies lack a comparator group
HCQ +/- azithromycin

- **Preprint Magagnoli, et al.** – HCQ in US VA
  - Retrospective cohort study of hospitalized pts
  - HCQ +/- azithromycin did not improve mortality or reduce need for mechanical ventilation
  - Tx with HCQ alone associated with an increased risk of mortality compared to standard care

- **Geleris, et al. NEJM.** – observational study
  - No significant association between HCQ use and primary composite endpoint of intubation or death
Mehra, et al. - Lancet

- Multinational registry analysis
  - No evidence of benefit of HCQ or CQ alone or in combination with a macrolide for in-hospital mortality
  - Data suggests tx is independently associated with increased risk of in-hospital mortality and de-novo ventricular arrhythmia
WHO Halts Hydroxychloroquine Trial Over Safety Concerns

May 25, 2020 · 4:34 PM ET

Coronavirus trial involving Oxford NHS staff paused following safety concerns

France Bars Use Of Hydroxychloroquine In COVID-19 Cases

May 27, 2020 · 12:39 PM ET
Scientists Question Validity of Major Hydroxychloroquine Study

Experts are demanding verification of data and methods used in a study of malaria drugs used to treat Covid-19. The study suggested the drugs may have increased deaths.

Guidelines for CQ/HCQ

• No high-quality evidence for efficacy of CQ/HCQ +/- azithromycin

• Guidelines recommend use only within context of a clinical trial or cite insufficient evidence to recommend for or against

• FDA cautions against use outside of a hospital setting or clinical trial given risk of dysrhythmias

• NIH recommends AGAINST high-dose CQ (600mg BID x 10d)

Lopinavir/ritonavir (LPV/r)

- NIH recommends against LPV/r or other HIV protease inhibitors except in context of a clinical trial
- In vitro activity against SARS but poor selectivity -> high levels of drug needed to achieve therapeutic levels, not likely to be tolerable, drug-drug interactions are a concern
- Cao, *et al.* NEJM. LPV/r vs. standard care failed to find clinical or virologic benefit (pts enrolled median 13d after sx onset)

Ribavirin

• In vitro activity against SARS limited and required high concentrations to inhibit viral replication
• Studies in SARS either inconclusive or demonstrated possible harm
  – Dose-dependent hematologic toxicity
  – Hepatic toxicity

Combo therapy – Hung, *et al.*

- Phase II RCT
  - Interferon B-1b* + LPV/r + ribavirin vs. LPV/r
  - Interferon only given to pts enrolled <7d after sx onset
  - No serious adverse events in combination group
  - Combo therapy associated with significant reduction in time to negative PCR, sx alleviation and LOS in pts started on tx <7d after sx onset
Umifenovir (Arbidol)

• Targets S protein/ACE2 interaction, inhibits membrane fusion of viral envelope

• In vitro data suggests activity against SARS and SARS-CoV-2

• Limited clinical data in COVID-19 – efficacy not established

• RCTs ongoing

Nafamostat and Camostat

- Camostat found in vitro to block viral entry of SARS-CoV-2
- Preprint report that nafamostat may block viral entry in vitro more efficiently than camostat
- Clinical trials ongoing

Remdesivir

• Inhibits viral RNA synthesis

• Investigational and not currently approved for any indication

• Preliminary data from NIAID and manufacturer-sponsored trials suggests potential benefit

• Randomized, double-blind, placebo-controlled trial (Wang, et al.) found no statistically significant clinical benefits

Preliminary Results of ACCT-1

• Double-blind, randomized, placebo-controlled trial in hospitalized patients with evidence of LRTI

• Remdesivir group had shorter time to recovery (median 11 vs. 15d)

• Mortality lower in remdesivir group but not statistically significant -> reported at day 14 currently
Topline Results of 2nd SIMPLE Trial

Press Releases

Gilead Announces Results From Phase 3 Trial of Remdesivir in Patients With Moderate COVID-19

– Study Demonstrates 5-Day Treatment Course of Remdesivir Resulted in Significantly Greater Clinical Improvement Versus Treatment with Standard of Care Alone –

June 01, 2020
Remdesivir

- NIH guidelines recommend for hospitalized patients with severe disease
  - SpO2 ≤94% on room air
  - Requiring supplemental O2, mechanical ventilation or ECMO

- NOT recommended for mild or moderate disease outside of a clinical trial
Obtaining remdesivir

- FDA Emergency Use Authorization

**Remdesivir Allocation**

- Oregon's Federal Redesivir Allocation: Patient Criteria and Hospital Distribution
- Hospital Agreement Form
- Last Mile Delivery User Guide for Shipping Remdesivir from OHA to Hospitals
- Fact Sheet for Health Care Providers: EUA of Remdesivir
- For patients:
  - Remdesivir Use for COVID-19 in Oregon – FAQ available in multiple languages
  - Fact Sheet for Patients and Parent/Caregivers – EUA of Remdesivir For Coronavirus Disease
    - Spanish Fact Sheet
Remdesivir EUA Criteria

- Suspected or confirmed SARS-CoV-2 infection by PCR
- Hospitalized
- Severe COVID-19 disease defined by ≥1 of following
  - SpO2 ≤94% on room air
  - Requiring supplemental oxygen
  - Requiring mechanical ventilation or ECMO
- Exclusion criteria include GFR <30, renal replacement therapy, ALT or AST ≥5x ULN
Remdesivir Compassionate Use

- [https://rdvcu.gilead.com/](https://rdvcu.gilead.com/)
- Not accepting new individual compassionate use requests
- Exceptions for pregnant pts and children <18yo with confirmed COVID-19 and severe disease
Convalescent Plasma

• Effect mediated via variety of mechanisms

• Early, limited data suggest a possible benefit

• Risks associated with the administration of plasma

• Multiple clinical trials ongoing

Guidelines - Convalescent Plasma

• NIH: Insufficient data to recommend for or against the use of convalescent plasma for treatment of COVID-19

• IDSA: recommended in context of a clinical trial for hospitalized patients
Convalescent Plasma

• Pathways available for use:
  – Clinical trials
  – Expanded access program
  – Individual patient emergency IND

Convalescent Plasma EAP

- [https://www.uscovidplasma.org/physicians-steps](https://www.uscovidplasma.org/physicians-steps)

- **Inclusion criteria**
  - ≥18yo (if <18yo, contact FDA for EIND)
  - Laboratory confirmed dx of COVID-19
  - Hospitalized
  - Severe or life-threatening COVID-19 or at high risk of progression to severe or life-threatening disease
  - Informed consent (form available at www.uscovidplasma.org)
Adjunctive therapies

- Immunomodulatory agents
  - Corticosteroids
  - IL-1 inhibitors (anakinra)
  - IL-6 inhibitors (sarilumab, siltuximab, tocilizumab)
  - Interferons
  - Janus kinase (JAK) inhibitors (baricitinib)
Corticosteroids

- **NOT** recommended with exception of ARDS due to COVID-19 in the context of a clinical trial

- Retrospective studies in COVID pneumonia show variable benefit but study limitations don’t allow determination of tx effect

- Previous data from SARS suggest potential harm (delayed viral clearance)
Immunomodulatory Agents

• Insufficient data to recommend for or against IL-1 or IL-6 inhibitors

• Clinical trials ongoing
Antibiotics

• **Mild**: NOT recommended
• **Moderate**: NOT recommended unless bacterial infection suspected

• **Severe**:
  – Surviving sepsis: suggested in pts requiring mechanical ventilation for respiratory failure (weak rec, low quality evidence)
  – NIH: insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication (BIII)

• **If started, re-assess daily for de-escalation**
Concomitant Medications

- Continue ACE inhibitors, ARBs, statins for pts already on these medications
- Pts taking NSAIDs for co-morbid condition should continue as previously directed by their provider
Resources

- NIH Treatment Guidelines: https://covid19treatmentguidelines.nih.gov/introduction/
- Clinical Trials: https://clinicaltrials.gov/
Thanks!

EVERYONE IS STRESSING ABOUT COVID-19

BUT I FOUND THE CURE