COVID-19 TREATMENTS

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TREATMENT

Review 30,000 level of initial treatments
Review mechanism of action
Future studies

HYDROXYCHLOROQUINE

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MECHANISM

- block viral entry into cells by inhibiting glycosylation of host receptors
- Proteolytic processing
- Endosomal acidification
- Immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.
- Chloroquine inhibits SARS-CoV-2 in vitro. Hydroxychloroquine has in vitro activity with a lower EC_{50} for SARS-CoV-2 compared with chloroquine after 24 hours of growth

Dose and Warnings

- 400mg Bid for day 1, 200mg Bid x 4 Days
- 200mg BID x 10 days
- Cardiac warning- QT prolongation
- Hypoglycemia
- Retinal warning
- Neuropsychiatric effects

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

Int J Antimicrob Agents. 2020 Mar 20

	Study Definitions	Comments
Design	Multiple centers in southern France Open-label non-randomized	- Main center patients received study drug - Other centers did not get study drug
Population	≥ 12 years old with PCR confirmed SARS-CoV-2	Very general inclusion criteria, so were all patients in this hospital with COVID-19 treated with hydroxychloroquine?
Intervention	Hydroxychloroquine 200mg TID x10 days	- Q fever dose - Higher dose than is being used in other studies
Primary Endpoint	Viral clearance at day 6	Some patients have a number reported for viral load (Cycle threshold), while others are only reported as positive or negative

	Control, n=16	Hydroxychloroquine, n=20
Age	37.3 ± 24 (range 10-75)	51.2 ± 18.7 (range 20-87)
Clinical status Asymptomatic URTI LRTI	 4 (25%) 10 (62.5%) 2 (12.5%)	 2 (10%) 12 (60%) 6 (30%)
Time between onset of symptoms and inclusion (days)	3.9 ± 2.8	4.1 ± 2.6

Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study

	Study Definitions	Comments
Design	Single center, observational, single arm	77 from main hospital, 3 from temporary COVIDunit
Population	Adults with PCR confirmed SARS-CoV-2 that received study drugs for **at least 3 days** with **6 days of follow up**	Did not tell us how any patients were excluded if they did not receive 3 days of study drug
Intervention	Hydroxychloroquine 200mg TID x 10 days Azithromycin 500mg x 1 dose then 250mg daily x 4 doses	

	N=80	Comments
Age	52.5 (IQR 42-62)	
Chronic conditions Hypertension Diabetes Chronic respiratory	 13 (16.3%) 9 (11.2%) 8 (10%)	Top 3 comorbidities
Clinical status Asymptomatic URTI LRTI	 4 (5%) 33 (41.2%) 43 (53.8%)	Heterogeneous population
Low NEWS	69 (92%)	Mild disease
Fever	12 (15%) 38.6 ± 0.12	Low fever and low rate of fever
Time between onset of symptoms and inclusion (days)	4.9 ± 3.6	Similar to last study, treated early

Summary

	N=80	Comments
Oxygen therapy	12 (15%)	
Transfer to ICU	3 (3.8%)	1.still in ICU 2. went to ICU but improved **1 died on the floor**
Length of Stay in ID unit (days)	4.6 ± 2.1	What about ICU/ floordays?
Time to Discharge(days)	4.1 ± 2.2 14 are still hospitalized	They made the requirements for discharge less stringent during the study 1. 2 negative swabs 2. 1 negative swab with 34Ct 3. Ct <34 but good clinical outcome

Summary

	First Publication		Second Publication
Treatment Arm	Hydroxychloroquine n=14	Hydroxychloroquine + azithromycin n=6	Hydroxychloroquine + azithromycin n=?
Baseline Viral Load (Ct)	25.4 ± 5.7	26.8 ± 2.5	23.6 ± 4.3 n=80
Negative PCR	8 (57.1%) at day 6	6 (100%) at day 6	83% at day 7 (n=50) 93% at day 8 (n=45)

- **Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial**
  - Inclusion/exclusion criteria are not clearly defined
  - Non-randomized, small sample size
  - Unclear why some patients had viral loads while others only had a negative or positive result
  - Huge age range, mild disease, no comorbidity data

- **Hydroxychloroquine-Azithromycin and COVID- 19, 80 patient observational study**
  - Results are not compared to hydroxychloroquine alone
  - Inclusion/ exclusion criteria are not clear
  - Assessment of negative viral load at day 7 and8
  - Authors changed the criteria for discharge and threshold for negative PCR as the study progressed
  - Even larger age range and mild disease

Treat early in patients with mild presentation to bring down viral load and prevent spread

Hydroxychloroquine effectiveness is encouraging

- Cumulative side effects (QTc prolongation, increased need to EKG)
- Short supply issues
- Additive effect of azithromycin is unclear

Hydroyxychloroquine Studies

Hydroxychloroquine is a chloroquine analog with

fewer drug-drug interactions.

Brown et al. Brief Summary of Potential SARS-CoV-2 Prophylactic and Treatment Drugs in the ED

on these results, they recommend an oral loading dose of

400 mg hydroxychloroquine sulfate twice daily on day one

followed by a maintenance dose of 200 mg twice daily for four days.

10 clinical trials in China evaluating the effect and safety of chloroquine in the treatment

Prelim data not released

Gao *et al* reported in a news briefing by the State Council of China that chloroquine

phosphate had “demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicenter clinical trials.

Jun *et al* conducted a prospective study of 30 SARSCoV-2 positive patients randomized to either standard

treatment or hydroxychloroquine. They found no difference

between the two groups with respect to median duration from

hospitalization to undetectable serum SARS-CoV-2, median

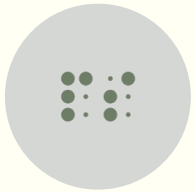
time to body temperature normalization, and development

of diarrhea and liver function test abnormalities.17

Lopinavir-Ritonavir

CAO ET AL CONDUCTED A RANDOMIZED, CONTROLLED, OPEN LABEL TRIAL OF LOPINAVIR-RITONAVIR

199 SARS-COV-2 HOSPITALIZED ADULT PATIENTS WITH AN O2 ≤ 94% ON ROOM AIR OR PARTIAL PRESSURE OF OXYGEN TO FRACTION OF INSPIRED OXYGEN LESS THAN 300



THIS COHORT WOULD THEN INCLUDE MILD, MODERATE AS WELL AS SEVERELY HYPOXIC PATIENTS.

NO DIFFERENCE IN 28 DAY MORTALITY

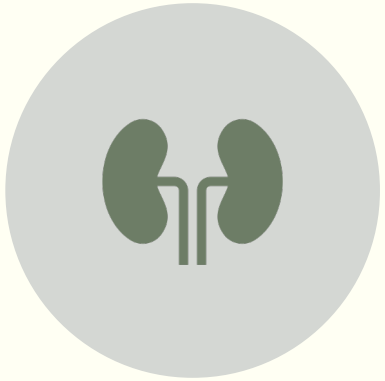
SIGNIFICANT GASTROINTESTINAL SIDE EFFECTS AND STOPPED THE LOPINAVIR-RITONAVIR EARLY IN 13 PATIENTS (13.8%) BECAUSE OF ADVERSE EVENTS.

THE LACK OF SURVIVAL BENEFIT AS WELL AS THE SIGNIFICANT SIDE EFFECTS MAKE THIS DRUG UNLIKELY TO BE USED IN THE ED AT THIS POINT.

IL-6 Blockers

THERE ARE ALSO ONGOING STUDIES WITH MONOCLONAL ANTIBODIES TOCILIZUMAB (CLINICALTRIALS.GOV: NCT04317092) AND SARILUMAB (CLINICALTRIALS.GOV: NCT04315298).

BOTH OF THESE AGENTS ARE INTERLEUKIN -6 RECEPTOR ANTAGONISTS THAT COULD THEORETICALLY ATTENUATE CYTOKINE AND ACUTE PHASE REACTANTS.



SARS-COV-2 DEPENDS ON THE ACE2 RECEPTOR FOR ENTRY, ANOTHER MULTICENTER PLACEBO-CONTROLLED TRIAL IS ENROLLING PATIENTS EVALUATING LOSARTAN (ANGIOTENSIN 2 RECEPTOR BLOCKER) IN PATIENTS REQUIRING HOSPITALIZATIONS (CLINICALTRIALS.

GOV: NCT04312009).

Future Presentation

Ribavarin	Interferon Alpha and B	Remdisivir
Favipiravir	Immunoglobulin therapy	Plasma therapy

JAMA. doi:10.1001/jama.2020.6019 Published online April 13, 2020.

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