CoVID-19:Pharmacological Therapy

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Pharmacological Therapy Chloroquine

- Potent *in vitro* activity against SARS-CoV-2 & small observational studies in vivo suggested more rapid viral clearance & inhibition of progression to pneumonia

Keyaerts Biochem Biophys Res Commun 2004
Gautret Science Direct doi: 10.1016/j.ijantimicag.2020.
Gautret . Int J Anitmicrob Agents 2020
Molina M´edecine et Maladies Infectieuses 2020
Chen J Zhejiang (Med Sci) 2020
Barbosa NEJM 2020

Hydroxychloroquine

- 16 Chinese treatment centres: n=150 in IIT analysis (75 HCQ) loading dose 1200 mg daily x 3 then maintenance 800mg daily (for 2-3 wks for mild to moderate or severe disease)
- Probability of negative conversion by 28 days in HCQ group was 85.4% (73.8-93.8%) & in std care group 81.3% (71.2-89.6%)
- Adverse events 30% on HCQ group vs 9%

Tang BMJ 2020;369:m1849 http://dx.doi.org/10.1136/bmj.m1849

HCQ with CoViD-19 pneumonia

- N= 181 (18-80 yrs) requiring O_2 but not ICU
- HCQ dose: 600 mg/day within 48 hrs of admission vs std care
- In weighted analyses survival without transfer to ICU at day 21 was 76% HCQ group vs 75%
- Overall survival at day 21: 89% in HCQ group vs 91%
- Survival without ARDS at day 21: 69% in HCQ group vs 74%
- No difference in number weaned from oxygen at day 21
- 10% on HCQ had ECG abnormalities requiring discontinuation

Mahévas BMJ 2020;369:m1844http://dx.doi.org/10.1136/bmj.m1844

Observational Study of Hydroxychloroquine

- n=1376; 58.9% received HCQ 600mg BD day 1, then 400mg daily x median of 5 days); 45.8% treated < 24 hrs after presentation & 85.9% < 48hrs hours
- HCQ patients were more ill at baseline median PF ratios 223 vs. 360
- In the main analysis, there was no significant association between HCQ use & intubation or death HR 1.04 (0.82-1.32).
- Results were similar in multiple sensitivity analyses.

Wang Lancet https://doi.org/10.1016/S0140-6736(20)31022-9

Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial

- N=1542 randomised to HCQ vs 3132 to usual care alone.
- No significant difference in 1° endpoint 28-day mortality (25.7% vs 23.5%) HR1.11 [0.98-1.26]; p=0.10
- There was also no evidence of benefit on hospital stay duration or other outcomes

Remdesivir

- DBRPT trial of in adults hospitalized with Covid-19 with LRTI: 200mg load then 100 mg daily x 9 days or placebo: n=1059
- Remdesivir group had a median recovery time of 11 (9-12) vs 15 days (13-19): rate ratio for recovery 1.32 (1.12-1.55) P<0.001
- Kaplan- Meier estimates of mortality by 14 days were 7.1% with remdesivir vs 11.9% (HR for death 0.70 (0.47-1.04).
- Serious adverse events remdesivir 21.1% vs 27.0%

Beigel NEJM DOI: 10.1056/NEJMoa2007764

Triple Therapy

- 14-days Keletra/Alluvia BD, ribavirin 400mg BD, 8 million IU interferon beta-1b x 3 on alternate days vs Keletra alone
- N=127; 86 randomly assigned to combination group
- Median days from symptom onset to start of therapy was 5 (3-7)
- Combination group had a significantly shorter median time to negative nasopharyngeal swab: 7 days [5–11] than controls (12 days [8–15]; HR 4·37 [1.86–10.24], p=0.0010)

Fan-Ngai Hung Lancet https://doi.org/10.1016/S0140-6736(20)31042-4

Treatment-dose systemic anticoagulation (AC)

- Included oral, SC, IV forms; adjusted for age, sex, ethnicity, BMI, hypertension, heart failure, atrial fib, type 2 diabetes
- 2,773 patients: 786 (28%) received systemic AC
- In-hospital mortality: AC 22.5% (median survival 21d) vs 22.8% (median survival 14d)
- In MV patients (N=395), in-hospital mortality was 29.1% (median survival 21d) vs 62.7% (median survival 9d)
- MVA: longer AC duration had a mortality risk (aHR 0.86/ day(0.82-0.89) p<0.001
- Bleeding events were similar

Paranjpe JACC https://doi.org/10.1016/j.jacc.2020.05.001

Corticosteroids

- Meta-analyses of CoVID 19 have not shown benefit
- In China methylpred associated with increased survival in ARDS (HR, 0.38; 95% CI, 0.20-0.72; P = .003)
- In a RCT in 17 Spanish ICUs: 139 of 277 patients with ARDS [PEEP ≥10, P/F< 200mmHg, FiO_2 ≥0.5] 24hrs post ARDS onset received IV dexamethasone 20mg x 5d then 10mg x 5d or routine care
  - Ventilator-free days higher (4.8 days [2.57-7.03]; p<0.0001) & 60d mortality 21 vs 36%: difference −15.3% [–25.9 to −4.9]; p=0.0047)
  - Adverse events not different

WHO https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf
Villar Lancet 2020
Huang NEJM 2020
Li Leukemia https://doi.org/10.1038/s41375-020-0848-3

Corticosteroids

- Patients admitted with SARS-CoV-2 pneumonia
- N= 396 (46.7%) consecutive patients received 1 mg/kg/day methylpred or equivalent vs 67 controls.
- Global mortality was 15.1%.
- Median time to CS from symptom onset: 10 days (IQR 8 -13)
- In-hospital mortality: 13.9% (CS) vs 23.9% OR 0.51 [0.27-0.96], p= 0.044 a 41.8% reduction RRR 0.42 [0.048-0.65]

Fernández Cruz medRxiv preprint doi: https://doi.org/10.1101/2020.05.22.20110544

Nutritional Interventions

- Vit C extracellular nutritional antioxidant quenches ROS
- Increasing intracellular Zn^{2+} with zinc-ionophores like pyrithione impairs replication SARS-CoV in cell culture
- Vit D is negative endocrine regulator of RAAS: SARS-CoV-2 downregulates ACE2 expression increasing inflammation & injury from PMNL infiltration & an unbalanced RAAS activation:
- Niacin: The presence of both Zn^{++} & NAD^{+} is imperative for function of SIRT1 which decreases levels of TNFa, IL1b and IL6

Liu Metabolism 2020 ChemRxiv.
Marik Crit Care 2018
te Velthuis PLoS Pathog 2020
Fontani *J Clin Gastroenterol Treat* 2017

Biologics: Tocilizumab

- Humanized monoclonal antibody for R arthritis; inhibits IL-6
- 21 patients with very elevated IL-6, 400mg stat (1 got 2 doses) led to rapid resolution of fever & improved gases, & CRP by day 5 & clearing of pulmonary infiltrates with no adverse events
- All had deteriorated despite routine therapies
- Listed as an option for severe/critical cases with elevated IL-6 in China
- Administer only with hyperinflammatory response; failure to respond to CS with high IL-6, rising CRP, ferritin, D-dimer, worsening hypoxaemia

Xu Pre Print. Available online: http://chinaxiv.org/abs/202003.00026
National Health Commission (NHC) of the People's Republic of China 2020
http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm

BCG & CoVID-19 Israel

- BCG vaccine administered to all newborns between 1955 & 1982 with > 90% coverage
- From1982 only to immigrants from high TB prevalence countries
- Testing performed only with symptoms compatible with COVID
- Of 72 060 tests, 3064 were from patients born between 1979 & 1981; 49.2% male; mean age, 40y
- 2869 born between 1983 &1985; 50.8% male; mean age 35 yrs
- No difference in positivity (11.7 vs 10.4%); P = .09 or in positivity/ 100000 (121 vs 100) P = .15
- 1 severe case in each group & no deaths

Hamiel JAMA doi:10.1001/jama.2020.8189

Convalescent Plasma

- 39 patients with severe to life-threatening COVID-19 received convalescent plasma vs retrospectively matched controls.
- Plasma recipients more: likely to remain unchanged or improve O_2 requirements by day 14: OR 0.86 (0.75~0.98) p=0.028
- Plasma recipients had improved survival: log-rank test: p=0.039
- Covariates-adjusted Cox model: plasma improved survival for non-intubated patients HR 0.19 (0.05 ~0.72); p=0.015) not intubated patients

Liu medRxiv preprint doi: https://doi.org/10.1101/2020.05.20.20102236

What Pharmacotherapy Would I Recommend

- Therapeutic anticoagulation (Xa guided) if D-dimer >1
- CS 200mg BD cortef equivalent x 5 days then 100mg BD
- Vitamin D 50,000 units stat
- Zinc 200 mg daily × 5 days
- Vitamin C 500 mg tds
- Nicotinic acid 100mg BD
- If clinical deterioration or requiring intubation on admission: Tocilizumab 400mg stat as well as CS
- The evidence for CQ, Alluvia, remdesivir etc is weak