COVID-19 and Rheumatology: A Critical Review of the Data
4/22/2020

Lecturers: Dr. Anisha Dua and Dr. Michael Putman

Talk Overview:
Review the literature on anti-rheumatic medications as treatment for COVID-19.

Talk conclusion:
As of Wednesday, April 22, no anti-rheumatic medications have shown definitive benefit in the treatment or prophylaxis of COVID-19. High quality randomized control trials are needed.

Rationale for use of anti-rheumatic medications in COVID 19
- **COVID-19**: single stranded RNA envelope virus that uses the host cell machinery to enter the host cell and replicate
- **Hydroxychloroquine (HCQ)** may mitigate COVID-19 by decreasing viral entry, increasing endosomal pH, decreasing MAPK phosphorylation, and disrupting post-translational modification.
- After COVID-19 infection, cytokine production may ramp up and potentially cause damage, similar to cytokine release syndrome. Increased IL-6 levels have been found in critically ill patients.

Evidence for anti-rheumatic medications:

**HCQ / Chloroquine**
- Rationale: Chloroquine or HCQ given to simian cells reduced viral entry and replication without excess cellular toxicity.
- Clinical data
  - 8 clinical studies
  - Used varying doses from HCQ 400mg daily up to 1200mg with studies from US, Italy, South America, China
  - Limitations: Most were small studies and most were not randomized control trials. In some trials, patients were not always confirmed COVID patients.
  - An early study by Gautret et al. (Int J Antimicrob Agents. 2020 Mar 20, Doi 10.1016) suggested improved viral clearance in patients given HCQ, however there were many methodological issues with this study.
  - Several other studies have not shown improved viral clearance, though one of those studies is a “pre-print,” meaning it has not yet been published in a peer-reviewed journal.
  - Unclear if HCQ decreases disease severity or ICU admissions.
    - Pre-print data from two studies have shown possible mild improvement in symptom duration, lymphopenia, and CRP with HCQ treatment.
    - Pre-print data from two other studies suggested an association between HCQ use and higher mortality, though unclear if this is due to unmeasured confounding variables.
  - High treatment doses of HCQ may be more associated with adverse events (diarrhea).
- Conclusions: Data are conflicting, methodological issues abound, and most data is in pre-print stage. Large, well-designed trials are needed.

**IL-6 inhibition**
- At present, there are no published randomized controlled trials of IL-6 inhibition in COVID-19.
- There are two reports of using tocilizumab and one report of siltuximab in patients with severe manifestations of COVID. These studies have described changes in lab parameters and clinical outcomes in treated patients, however neither had a control group so it is difficult to draw conclusions.

**Suspected benefit**: anti-rheumatic drugs without known (or minimal) clinical trial data but suspected benefit
- Baricitinib. Lancet article with artificial intelligence predicting that baricitinib might be helpful because it would inhibit multiple pathways important for COVID pathogenesis
- Anti-TNF-α. Consider that this might be helpful in similar way as to IL-6
- IL-1β inhibition for treatment of cytokine storm

**Rheumatology patients are not immune to COVID**
- Global rheumatology alliance data (Gianfrancesco: Lancet Rheum, 4/16/2020) reports that patients with rheumatologic conditions still get COVID 19.