Full title of manuscript (maximum of 20 words): **Treating Covid-19 at the Inflection Point**

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Dr. Cron serves as a consultant to SOBI. Dr. Chatham has served as a consultant to SOBI.

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Short running head (maximum of 4 words): Covid-19 Treatment Inflection Point

We appreciate the interest by Moura and colleague in our editorial regarding the role of the rheumatologist during the Covid-19 pandemic (1). The letter by Drs. Carlos Antonio Moura and Ana Luísa Cerqueira de Sant'Ana Costa emphasizes the need to understand mechanisms of disease underlying the more serious complications of Covid-19 infection as well as provide the best treatment possible to large numbers of seriously ill patients during a global pandemic (2). Many of the treatments administered to date under crisis conditions in uncontrolled fashion have been based upon at least some mechanistic rationale as reflected in the table accompanying their letter. Well-designed randomized controlled trials (RCT) take time to design, undergo ethics board review, and enroll, and some of these are beginning to result. While the National Institutes of Health sponsored RCT with remdesivir has been reported to shorten the time to recovery and duration of hospitalization (3), it is becoming increasingly apparent that the addition of immunomodulation will likely be required to forestall progression of respiratory failure, treat underlying vascular inflammation, and significantly impact survival (1, 4). Until definitive RCT can be completed, non-randomized cohort studies may help to inform which and at what stage of disease currently available immune modulating therapies are likely to be helpful or not. To date, such studies indicate that antimalarials such as hydroxychloroquine do not appear to significantly impact either the need for invasive mechanical ventilation or survival (5); whether their known impact on TLR signaling might be of benefit in earlier pre-hospital stages of disease remains to be determined in the context of current RCT. As noted by Moura and de Sant'Ana Costa, recently published small cohort control studies report encouraging results with JAK inhibitors (6) and anti-interleukin-6 receptor (IL-6R) monoclonal antibodies (7) with regard to decreasing the need for mechanical ventilation and survival. Published cohort studies showing similar encouraging results with anakinra (IL-1R antagonist) are also emerging and would be an appropriate addition to the table (8). Collectively, these published experiences can help guide both the care of seriously ill patients in settings where trial enrollment is not an option

as well as the design of RCT that will provide the best “calculation of the probability” of the utility of immune modulators in managing severe complications of Covid-19.

As suggested by Moura and de Sant’Ana Costa, there is likely an appropriate window of opportunity to obtain maximal benefit of immunomodulatory therapy (2). While up to 25% of SARS-CoV-2 infected adults are asymptomatic, the early clinical features of Covid-19 infection include constitutional symptoms, fever, headache, and malaise, and as SARS-CoV-2 sets up “shop” in the lower respiratory tract, cough can be an early manifestation of disease. For many of these symptomatic Covid-19 individuals, the illness may temporarily wane between days 3 and 5 following symptoms. Somewhere between days 5 and 7 of illness (Figure), there is an inflection point where the disease worsens with some developing a more significant flu-like illness that can be ridden out at home, and others becoming acutely hypoxic necessitating hospitalization (9). While the innate immune response is triggered early on, the adaptive immune system has already been engaged by the time that this more severe respiratory stage of disease emerges (Figure). In those who are developing acute respiratory distress syndrome, there is likely a cytokine storm syndrome (CSS) evolving from an ongoing interaction of the innate and adaptive immune cells resulting in an inappropriate amplification of pro-inflammatory cytokines (10). It is at this stage, just prior to the need for intubation/mechanical ventilation and intensive care, that immunomodulatory approaches should be strongly considered, particularly in those hypoxic Covid-19 patients with laboratory features of CSS, such as hyperferritinemia and elevated C-reactive protein, D-dimer, and lactate dehydrogenase (1, 4).

In addition to potentially effective anti-viral treatments, the addition of CSS-directed therapies at the inflection point of disease has the greatest potential to decrease mortality from Covid-19.

Which of the various proposed anti-CSS therapies will be most beneficial remains unclear at present prior to RCT results. However, promising reports of small and moderate sized case series and cohort comparison studies suggest that several targeted approaches to diminish pro-inflammatory cytokines will be effective at reducing Covid-19 mortality, particularly when given at the inflection point between the anti-viral immune response and the beginning of the CSS. Rheumatologists can help their clinical colleagues determine which hospitalized Covid-19-infected patients are developing a CSS, and how best to manage the CSS with immunomodulation to help save lives (1).

Figure Legend

Figure. The Covid-19 Inflection Point of Illness

A graphic depiction of the course of illness, for the up to 20% of Covid-19 individuals who develop a cytokine storm syndrome (CSS) and respiratory distress requiring hospitalization, presents severity of illness along the Y-axis and time in days along the X-axis. The participation of both the innate and adaptive immune response are presented as respective triangles during different phases of disease. The early stages of infection (<5 days of symptoms) gives rise to a more prominent respiratory phase in those with early signs of CSS, such that an inflection point of illness occurs typically between days 5 and 7 of illness. This is the time where targeted immunomodulatory therapy will likely be most beneficial to lower mortality (dashed arrow). ARDS = acute respiratory distress syndrome; MODS = multi-organ dysfunction syndrome.

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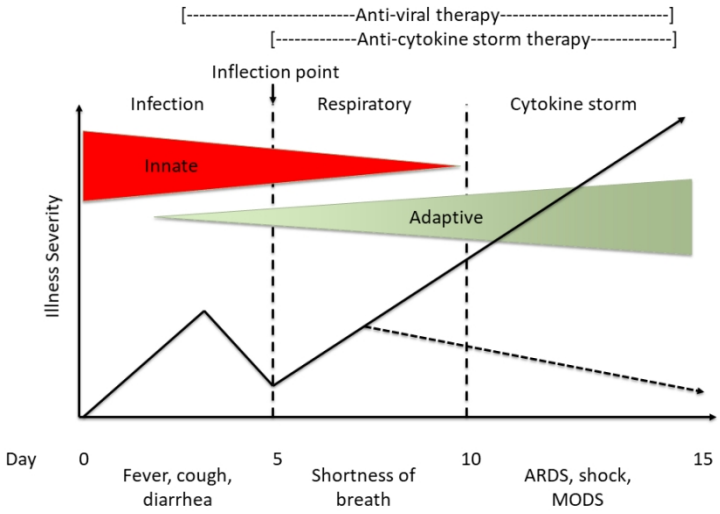

The Covid-19 Inflection Point of Illness

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