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LIMITED IMMUNE RESPONSE DATA FOR EARLY COVID-19 HAS GREATLY HINDERED OUR UNDERSTANDING OF DISEASE PATHOGENESIS: DAILY MEASUREMENT OF IL-1beta, IL-6 AND TNFalpha WOULD HAVE HELPED GREATLY

One of the greatest difficulties in unraveling COVID-19 pathogenesis has been the few longitudinal studies that give clear evidence of changes in immune cell proportions and cytokine and chemokine production during the early/mid symptomatic phase. To a great extent this is due to the way COVID-19 therapy has been handled in many countries around the world. People who believe they are suffering symptoms of COVID-19 have been told to stay at home and so medical systems have little knowledge of the early symptomatic phase of COVID-19.

Whilst the study of Lucas et al. (1) measures cellular and cytokine responses from day 1 of symptom onset, patients were grouped over days 1-5 and 6-10. From this we cannot glean any clues as to daily changes in cytokine profiles. We are left to wonder why some individuals suffer severe flu-like early symptoms, but avoid transition to the pulmonary phase, whilst others who have moderate early symptoms, transition to the pulmonary phase and then (perhaps) on to severe COVID-19.

These observations beg the question as to what is responsible for the symptom severity of the early/mid symptomatic phase over the first 5 or so days from symptom onset. From basic principals, symptoms must be due to physical cellular damage due to virus propagation, interference with essential cellular pathways or the induction of pro-inflammatory cytokines such as IL-6 and TNFalpha, that result in a sickness response.

Perhaps the closest we can get to addressing cytokine profiles associated with early symptoms is to consider flu infection. Of the so-called early cytokines produced at the site of infection, IFNα, TNFα, IL-1ß, IL-6, the neutrophil chemoattractant IL-8 and monocyte-attracting chemokines, are elevated (2).These cytokine are produced as part of the innate immune response to infection and one assumes that a similar response (with the known exception of the weaker type 1 interferon response) will be apparent in COVID-19.

However, unlike flu, where severity is equated with the magnitude of the early cytokine response, COVID-19 is in effect two diseases (3), a confusingly assigned ‘symptomatic phase ’that often resolves and a later response where patients transition to a hyper-inflammatory, life-threatening phase.

To gain a better understanding, the sequential daily measurement of at least IFNα, TNFα, IL-1ß and IL-6, would have been most useful. One assumes that there must be an increase in the early symptomatic phase due to innate signalling and inflammasome activation by PAMPs (Pathogen Associated Molecular Patterns) and then a fall, as symptoms resolve. A secondary rise in IL-6 after around a week from symptom onset has been recorded and this appears to herald the onset of the early pulmonary phase (in effect the hyper-inflammatory disease that may resolved for some individuals).

A secondary rise in IL-6 for individuals where initial flu-like symptoms were mild might suggest that the initial innate response to SARS-CoV-2 was weak. IL-1beta and IL-6 measurement may have confirmed this as these cytokines should reflect inflammasome activation.

If poor initial innate immune system activation is the reason for a mild symptomatic phase, then intracellular viral infection may be greater. The continued viral replication may result in accumulation of viroporin membrane structures and these may provide effective inflammasome activators in infected cells (4).

Monocytes have been shown to undergo pyroptosis (5) in response to SARS-CoV-2 infection (inflammasome-driven cell death with characteristic of necrosis) and this event may follow a rise in IL-6 that marks the transition to the early pulmonary phase. The release of PAMPs and DAMPs (Damage Associated Molecular Patterns) due to a burst of cell death 5-7 days from symptom onset may result in the further activation of immune and tissue cells alike. A prominent cell type here is likely to be the mast cells, as indicated previously (6).

Knowing the exact timing for the end of the symptomatic phase and the beginning of the pulmonary phase by carefully measuring daily cytokine/chemokine changes is essential to staging of therapy. Be assured, COVID-19 is an eminently treatable disease. This understanding is supported by the work of Dr Shankara Chetty (7) and indeed others. Dr Chetty has treated well over 4000 patients and not lost one. The key is to time therapy in the form of a corticosteroid, an antihistamine and a leukotriene receptor blocker, to coincide with the transition between the late symptomatic phase and the early pulmonary phase (7).

An inability to develop therapy to treat COVID-19 in its early stages has been a catastrophic failure in medical practice. The societal and economic cost of this failure is incalculable.

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