Comment
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Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed

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With more than 81 000 deaths worldwide from coronavirus disease 2019 (COVID-19) by April 8, 2020,[1] it is incumbent on researchers to accelerate clinical trials of any readily available and potentially acceptably safe therapies that could reduce the rising death toll. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains access to host cells via angiotensin-converting enzyme 2, which is expressed in the type II surfactant-secreting alveolar cells of the lungs.[2] Severe COVID-19 is associated with a major immune inflammatory response with abundant neutrophils, lymphocytes, macrophages, and immune mediators. Which mediators are most important in driving the immune pathology remains to be elucidated. Deaths from COVID-19 are chiefly due to diffuse alveolar damage with pulmonary oedema, hyaline membrane formation, and interstitial mononuclear inflammatory infiltrate compatible with early-phase adult respiratory distress syndrome (ARDS).[3] Prevention of ARDS and death in patients with COVID-19 is a pressing health emergency.

Anti-tumour necrosis factor (TNF) antibodies have been used for more than 20 years in severe cases of autoimmune inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, or ankylosing spondylitis. There are ten (as reported on Sept 29, 2019) US Food and Drug Administration approved and four off-label indications for anti-TNF therapy,[4] indicating that TNF is a valid target in many inflammatory diseases. TNF is present in blood and disease tissues of patients with COVID-19[5] and TNF is important in nearly all acute inflammatory reactions, acting as an amplifier of inflammation. We propose that anti-TNF therapy should be evaluated in patients with COVID-19 on hospital admission to prevent progression to needing intensive care support.

There is evidence of an inflammatory excess in patients with COVID-19. Lung pathology in COVID-19 is characterised by capillary leakage of fluid and recruitment of immune-inflammatory lymphocytes, neutrophils, and macrophages,[6] implying a role for adhesion molecules, chemokines, and cytokines targeting vascular endothelium.

Cytokine upregulation is documented in COVID-19. In patients with COVID-19, there is upregulation of pro-inflammatory cytokines in the blood, including interleukin (IL)-1, IL-6, TNF, and interferon γ,[7,8] and patients in intensive care units have increased concentrations of many cytokines. Preliminary data from Salford Royal Hospital and the University of Manchester in the UK document the presence of proliferating excess monocytes expressing TNF by intracellular staining in patients with COVID-19 in intensive care (Hussell T, Grainger J, Menon M, Mann E, University of Manchester, Manchester, UK, personal communication). Available cytokine data on immunology and inflammation in COVID-19 are summarised in the appendix.

See Online for appendix

Initial reports comprising a trial of 21 severe and critical COVID-19 patients in China (ChiCTR2000029765) and a case study from France[9] of clinical benefit with the anti-IL6 receptor antibody[10] tocilizumab in COVID-19 suggest that cytokines are of importance in the "cytokine storm" and further controlled clinical trials are in progress. Although there are many potential drug candidates for reducing inflammation in COVID-19, only a few drugs such as the anti-TNF antibodies infliximab or adalimumab are potentially effective, widely available, and have a well established safety profile.

The potential role of anti-TNF therapy thus warrants consideration. Preclinical studies suggest that the response to severe respiratory syncytial virus (RSV) and influenza in mice is ameliorated by anti-TNF therapy,

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which reduces weight loss, disease duration, and cell and fluid infiltrate.[11] This research suggests a potential rationale for use of anti-TNF therapy in viral pneumonia, especially given the known mechanism of action of TNF and the reversal of TNF-induced immunopathology by TNF blockade in multiple diseases. It is known TNF is produced in most types of inflammation, especially in the acute phase, and is important in the coordination and development of the inflammatory response. However, too much production of TNF for too long becomes immune suppressive.[12] Blockade of TNF alone is clinically effective in many circumstances and diseases, despite the presence of many other pro-inflammatory cytokines and mediators. There is evidence of a "TNF dependent cytokine cascade" in rheumatoid arthritis tissue and upon bacterial challenge in baboons.[13,14] Thus, if TNF is blocked, there is a rapid (ie, <12 h) decrease of IL-6 and IL-1 concentrations in patients with active rheumatoid arthritis[15] and, importantly, a reduction of adhesion molecules, vascular endothelial growth factor, which is also known as vascular permeability factor, denoting its importance in capillary leak.[15-19] Furthermore, a reduction in leucocyte trafficking occurs in inflamed tissues of joints due to reduction in adhesion molecules and chemokines[20] with reduction in cell content and exudate. Finally, after anti-TNF infusion tissue TNF is reduced as it passes into the blood bound to the anti-TNF antibody. Blood concentrations of immunoreactive, but biologically inactive, TNF increases more than ten times after infusion.[15] For these reasons it is possible that a single infusion of anti-TNF antibody might reduce some of the processes that occur during COVID-19 lung inflammation, reducing TNF and other inflammatory mediators, cellularity, and exudate.

What would be the best time for intervention with anti-TNF therapy in patients with COVID-19? We postulate that the earlier the better after hospital admission might be the answer because patients will already have initiated anti-viral immunity for several days. There is a balance to be struck between stage of intervention and ensuring patients are at sufficient risk of a poor outcome and can be appropriately monitored. We propose that initial assessment of anti-TNF therapy in clinical trials should be in patients with moderate disease admitted to hospital and who require oxygen support but not intensive care. If this treatment approach proved beneficial with a good safety profile, treatment in the community for people identified as being at high risk of progressing to hospital admission might be considered. The range of available formulations and administration routes of anti-TNF products could facilitate this treatment approach.

Is there a trade-off between immunity and virus clearance? The use of powerful anti-inflammatory drugs in acute viral diseases has to be approached with caution because of the risk of increasing viral replication or bacterial infections. For lung viral infections, the higher the infectious dose, the greater the tissue damage from viral replication and the ensuing immune response. In animal models that resemble lung viral infection in humans, the immune response to the virus is so great that even a moderate reduction in inflammation is beneficial—eg, mice with severe pneumonia from RSV or influenza benefit from anti-TNF treatment without compromising viral clearance[11] because more of the lung architecture is preserved.

However, concerns about safety are important when considering new therapy. Would anti-TNF therapy increase the risk of bacterial or fungal super-infections? After respiratory viral infection, superinfections with other organisms occur at the most severe end of the disease spectrum. Many research groups have elucidated the mechanisms responsible[21] and anecdotal evidence suggests that bacteria might have a role in in COVID-19,[5,22] although this remains to be confirmed. Bacteria gain a foothold faster in a lung that is damaged. Experimental studies suggest that if the duration of inflammation is limited, with its associated collateral lung damage, then bacterial superinfection is reduced.[23] There is concern that anti-TNF therapy might increase the risk of bacterial infection.[24] Yet two randomised studies in critically unwell patients with septic shock[25,26] showed that monoclonal anti-TNF therapy had good safety data with no evidence of increased secondary bacterial infections in the anti-TNF treated group. In an observational trial in rheumatoid arthritis patients with serious infections, the risk of sepsis and death was reduced in patients on TNF inhibitors compared with those on synthetic disease-modifying anti-rheumatic drugs (DMARDS).[27] 46 (11%) of 399 patients on TNF inhibitors developed sepsis after serious infection, of whom 20 (43%) died, compared with 74 (17%) of 444 patients on DMARDS who developed sepsis, of whom 54 (74%) died.[27] Paradoxically, another class of TNF inhibitor, a TNF-R2

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Ig-Fc fusion protein, etanercept, was associated with moderately increased mortality in a randomised trial of this treatment for sepsis,[28] possibly due to its faster off-rate for TNF potentially resulting in some redistribution and bioavailability of pathogenic TNF rather than its clearance.

There has been interest as to whether the safety of anti-TNF therapy in patients with COVID-19 might be gleaned from analysis of the course of COVID-19 in patients with inflammatory bowel disease (IBD) or rheumatoid arthritis who are already on anti-TNF treatment. As of April 6, 2020, on SECURE-IBD, a coronavirus and IBD reporting database with a register of outcomes of IBD patients with COVID-19, there were 116 patients on anti-TNF therapy alone, 99 of whom recovered without hospitalisation and one patient died. By contrast, about half of 71 patients on sulfasalazine/mesalamine recovered without hospital admission and six patients died. Thus IBD patients with COVID-19 on anti-TNF therapy do not fare worse than those treated with other drugs, but there are insufficient data to make conclusions about a better outcome.

We believe there is sufficient evidence to support clinical trials of anti-TNF therapy in patients with COVID-19. With an average of 2 days between hospital admission and ARDS,[7] we propose anti-TNF therapy should be initiated as early as is practicable. If there is preliminary evidence of benefit and safety of anti-TNF therapy in hospitalised patients, we suggest consideration should be given to out of hospital treatment for patients with COVID-19 at high risk, such as older people and those with pre-existing conditions, and who can be monitored appropriately.

MF and RNM have held patents, now expired, on use of infliximab and methotrexate in inflammatory arthritis and have received royalties from Johnson and Johnson, AbbVie, Amgen, and UCB, none of which are for respiratory or critical care. The financial assets of the Kennedy Trust for Rheumatology Research were largely derived from patent royalties on anti-TNF antibodies. JNW is a General Partner at Laterell Venture Partners, a role unrelated to the topic of this Comment. STH is Non-Executive Board Director (NED) and a shareholder of Synairgen. Synairgen is conducting a clinical trial of inhaled IFN β in COVID-19 patients, but this is unrelated to this Comment. STH has played no direct role in the Synairgen trial other than his role as a NED. STH has no direct interests in anti-TNF or any other therapeutics referred to in this Comment. GW receives directors fees that include options to shares as Founder and Director of Bicycle Therapeutics plc unrelated to the topic of this Comment and was a Founder of Cambridge Antibody Technology, which in the 1990s co-developed the anti-TNF antibody adalimumab, and pre-2003 advised Peptech and Domantis on their anti-TNF developments and patents. GW is a Trustee of the Kennedy Trust for Rheumatology Research, for which the financial assets were largely derived from patent royalties on anti-TNF antibodies. DR reports personal fees for consultancy on drug safety from GlaxoSmithKline unrelated to the topic of this Comment. MR and TH declare no competing interests.

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For **SECURE-IBD** see https://covidibd.org/

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