

Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment



The COVID-19 pandemic continues to wreak havoc on global health-care systems and to claim an increasing number of lives. Although some treatments have shown promise, including dexamethasone and remdesivir, problems remain with access to medication and high mortality despite treatment. Patient selection also appears to be critical, with some patient groups benefitting from treatment, but not others. One potential treatment that deserves higher priority in COVID-19 trials, based on the documented evidence of its effects, is the biological agent anti-TNF.

Feldmann and colleagues¹ described the rationale for trialling anti-TNF therapies in COVID-19. These therapies neutralise TNF, a major component of the cytokine response that is part of the damaging excess inflammatory phase of COVID-19, which is termed hyperinflammation or cytokine release syndrome. This hyperinflammatory response in COVID-19 is characterised by elevated concentrations of serum TNF, interleukin (IL)-6, and IL-8, but relatively little IL-1.² However, IL-1 has a short serum half-life, and mononuclear transcriptome data show that genes and pathways upregulated by TNF, IL-1 β , and type I interferon predominate.³ A major component of deteriorating lung function in patients with COVID-19 is capillary leak, a result of inflammation driven by key inflammatory cytokines: TNF, IL-1, IL-6, and vascular endothelial growth factor. Administration of anti-TNF to patients for treatment of autoimmune disease leads to reductions in all of these key inflammatory cytokines.^{4,5} It is therefore conceivable that anti-TNF therapy could reduce inflammation-driven capillary leak in COVID-19 and have a major impact on the need for ventilation and mortality.

The concept of blocking cytokines as a therapy for COVID-19 is not new. Anti-IL-6 receptor therapy has been given much attention, with observational studies of IL-6 blockade showing promise. However the first randomised, controlled, phase 3 trial of tocilizumab in COVID-19 did not show a difference in clinical status or death. An exploratory phase 2 trial of sarilumab also did not show improvement in clinical outcomes.

Anti-TNF therapy differs greatly from anti-IL-6 therapy. In synovial tissue cultures from patients with rheumatoid

arthritis, TNF blockade leads to downregulation of other pro-inflammatory mediators, including IL-1, IL-6, and granulocyte-macrophage colony stimulating factor within 24 h.^{6,7} Serum concentrations of cytokines and acute phase proteins are also downregulated after administration of anti-TNF therapy in patients with rheumatoid arthritis, including IL-6, IL-1 receptor antagonist, serum amyloid A, haptoglobin, and fibrinogen, again many within 24 h.^{4,5} Clotting biomarkers are also rapidly downregulated, with significant reductions in D-dimer and pro-thrombin fragments seen within 1 h of anti-TNF therapy.⁷ The same is not documented for anti-IL-6 or anti-IL-1 therapies. In addition, anti-TNF blockade is effective in many autoimmune and inflammatory diseases, ten indications of which have approval from the US Food and Drug Administration, and this approach is used widely off label. By contrast, IL-6 blockade is approved only in rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, and chimeric antigen receptor-modified T cell cytokine release syndrome.

Observational clinical data support the potential of anti-TNF therapies as a treatment for COVID-19. Data from the SECURE-IBD registry suggest that when patients with inflammatory bowel disease develop COVID-19, those on anti-TNF therapies do just as well and possibly better than those on alternative agents. Anti-TNF therapy was found to be inversely associated with the composite outcome of death or hospital admission for COVID-19 (adjusted odds ratio [OR] 0.60 [95% CI 0.38–0.96], $p=0.03$).⁸ However anti-TNF therapy did not have an effect on the composite of intensive care admission, ventilation or death, and death alone.

The COVID-19 Global Rheumatology Alliance registry has found similar but perhaps clearer results. Data from 600 patients with rheumatic disease showed that the use of anti-TNF therapy, either alone or in combination with other immunomodulatory drugs, compared with no disease-modifying antirheumatic drugs, was associated with a lower rate of hospital admission for COVID-19 (adjusted OR of 0.40 [95% CI 0.19–0.81], $p=0.01$).⁹ When anti-TNF therapy was used as monotherapy the adjusted OR was 0.30 (95% 0.11–0.79, $p=0.01$) for hospital

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For the SECURE-IBD registry see
covidibd.org

For the COVID-19 Global
Rheumatology Alliance registry
see rheum-covid.org

For more on the phase 3 trial of
tocilizumab see <https://www.roche.com/dam/jcr:6d8de90d-2e31-43c8-b4e1-0a24a2675015/en/29072020-mr-covacta.pdf>
For more on the phase 2 trial of
sarilumab see <https://ml-eu.globenewswire.com/Resource/Download/cdc6dbec-2fac-4ad9-815c-bf129fca722>

admission. A smaller series of 77 patients with COVID-19 using immunomodulatory drugs for pre-existing medical conditions found similar results. 48% of patients required ventilator support and 12% died. However, no patients on anti-TNF therapy required ventilator support or died. Notably, 40% of patients on non-TNF biologics required ventilator support and 13% died, highlighting the importance of specific TNF blockade.¹⁰

There are limitations with the data from SECURE-IBD and the COVID-19 Global Rheumatology Alliance registries. Comparators are other patients with rheumatic disease or inflammatory bowel disease. These patients might respond differently to COVID-19 due to chronic changes in their immune system. It is therefore unknown whether the anti-TNF therapy results found in these registries are generalisable to the public. The patients in the registry have also probably been on anti-TNF therapies for some time before COVID-19. It is uncertain whether first administration of anti-TNF during infection would yield the same results.

There are a small number of case reports on the use of anti-TNF therapy in the acute setting in patients with COVID-19. Two cases have been reported of patients with inflammatory bowel disease flares and concomitant COVID-19 infection in which administration of infliximab led to marked improvement of COVID-19 symptoms, chest imaging, inflammatory markers, and cytokine concentrations.^{11,12} In another case series of seven patients without inflammatory bowel disease treated with infliximab for COVID-19, six patients recovered from the infection and all six had reductions in concentrations of IL-6 and C-reactive protein, reflecting downregulation of inflammation beyond TNF blockade.¹³

Surprisingly, very few studies are examining anti-TNF therapy as a potential treatment for COVID-19. The CATALYST randomised trial (ISRCTN40580903) is investigating the use of infliximab in patients admitted to hospital with clinical features of COVID-19. This trial is recruiting in the UK, where rates of hospital admission are now low and accrual rates are commensurately low. A pilot study in 17 patients is ongoing at Tufts Medical Center (Boston, MA, USA; NCT04425538) and another pre-hospital study is planned in the UK (ISRCTN33260034) to establish whether anti-TNF therapy can prevent progression to severe illness. These trials face considerable recruitment challenges because of the vast array of therapies under investigation.

There is great imperative to find effective treatments for COVID-19. The small effect size of the most promising agents so far means that we need to continue the search for agents with greater efficacy. The potential of anti-TNF therapy as a treatment for COVID-19 is supported by both biological plausibility and observational clinical data. Few current treatments under investigation have this level of supportive evidence. There is a long history of safe use of anti-TNF therapy in a diverse range of diseases, and supply is plentiful with many originator products available as well as many biosimilars. Anti-TNF therapy now has huge potential. We need to urgently investigate its value through prioritisation of clinical trial resources worldwide.

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