

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

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The coronavirus pandemic continues to wreak havoc on global healthcare systems and claim an increasing number of lives. While some treatments have shown promise including dexamethasone and remdesivir, there remains problems with access to medication and a high mortality despite treatment.^{1,2} Patient selection also appears critical with some patient groups benefiting from treatment and not others. One potential treatment that deserves more priority study is the biologic agent, anti-tumour necrosis factor (anti-TNF).

Feldmann and colleagues previously described the rationale for trialling anti-TNF therapies in coronavirus disease-2019 (COVID-19).³ These therapies neutralise TNF, a major component of the cytokine response that is part of the damaging excess inflammatory phase of COVID-19. This inflammatory response is characterised by elevated levels of serum TNF, IL-6, IL-8 but relatively little IL-1.⁴ However, IL-1 has a short serum half-life and mononuclear transcriptome data shows genes and pathways upregulated by TNF, IL-1 β and type I interferon predominate. A major component of deteriorating lung function in 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.⁵ It is therefore conceivable that anti-TNF could reduce inflammatory driven capillary leak in COVID-19 and have a profound 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 therapy has been given much attention with observational studies of IL-6 blockade

showing promise. However the first randomised phase III controlled trial of tocilizumab in COVID-19 did not show a difference in clinical status or death (MARGIN LINK: <https://www.roche.com/dam/jcr:6d8de90d-2e31-43c8-b4e1-0a24a2675015/en/29072020-mr-covacta.pdf>). An exploratory phase II trial of the anti-IL-6 receptor antibody sariliumab also did not show improvement in clinical outcomes (MARGIN LINK: <https://ml-eu.globenewswire.com/Resource/Download/cdc6dbee-2fac-4ad9-815c-bf129fc1a722>).

Anti-TNF therapy differs greatly from anti-IL-6 therapy. In synovial tissue cultures from patients with rheumatoid arthritis (RA), TNF blockade leads to downregulation of other pro-inflammatory mediators including IL-1, IL-6 and granulocyte-macrophage colony stimulating factor (GM-CSF) within 24 hours.^{8,9} Serum levels of cytokines and acute phase proteins are also downregulated after administration of anti-TNF in patients with RA, including IL-6, IL-1 receptor antagonist, serum amyloid A, haptoglobin and fibrinogen, again many within 24 hours.^{5,10} Clotting biomarkers are also rapidly downregulated with significant reductions in D-Dimer and pro-thrombin fragments seen within one hour of anti-TNF therapy.¹¹ The same is not documented for anti-IL-6 therapies. In addition, anti-TNF blockade is effective in many autoimmune/inflammatory diseases, ten of which have FDA approval and it is used widely off label. In contrast, IL-6 blockade is effective only in rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis and chimeric antigen receptor-modified T cell (CAR-T) cytokine release syndrome.

Observational clinical data supports the potential of anti-TNF as a treatment for COVID-19. Data from the SECURE-inflammatory bowel disease (IBD) COVID-19 registry (MARGIN LINK: covidibd.org) suggests that when patients IBD become infected with COVID-19, those on anti-TNF therapies do just as well and possibly better than those on alternate agents. Anti-TNF was found to be inversely associated with the composite outcome of death or hospitalisation for COVID-19, adjusted odds ratio (aOR) 0.60 (95% confidence interval (CI) 0.38–0.96, $P=0.03$).¹⁰ However anti-TNF use did not have an effect on the composite of intensive care admission, ventilation or death and death alone.

The COVID-19 Global Rheumatology Alliance (C19-GRA) registry has found similar results. (MARGIN LINK: rheum-covid.org). Data from 600 patients with rheumatic disease showed that the use of anti-TNF, either alone or in combination with other immune modifying agents, compared to no disease modifying anti-rheumatic drugs, was associated with a lower rate of hospitalisation for COVID-19 (aOR of 0.40, 95% CI 0.19–0.81, $P=0.01$)¹¹. When anti-TNF was used as monotherapy there was an aOR of 0.30 (95% 0.11–0.79, $P=0.01$) for hospitalisation. A smaller series of 77 patients with COVID-19 using immunomodulatory drugs for pre-existing medical conditions found similar results. Overall rates for ventilation and mortality were 48% and 12% respectively. However, no patients on anti-TNF therapy required ventilator support or died. Of particular interest is that rates of ventilation and mortality amongst patients on non-TNF biologics was 40% and 13% respectively, highlighting the importance of specific TNF blockade.¹²

There are limitations with the registry data from SECURE-IBD and the C19-GRA. Comparators are other patients with rheumatic disease or IBD. These patients may respond differently to COVID-19 due to chronic changes in their immune system. It is therefore unknown whether the anti-TNF results found in these registries are generalisable to the public. The patients in the registry have also likely been on anti-TNF therapies for some time prior to 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. There are two cases reported of patients with IBD flares and concomitant COVID-19 infection where administration of infliximab led to marked improvement of COVID-19 symptoms, chest imaging, inflammatory markers and cytokine levels.^{13,14} In another case series of 7 patients without IBD treated with infliximab for COVID-19, 6 patients recovered from the infection and all 6 had reductions in levels of IL-6 and CRP, reflecting downregulation of inflammation beyond TNF blockade.¹⁵

Surprisingly, there are very few studies examining anti-TNF as a potential treatment for COVID-19. The CATALYST randomised trial (ISRCTN40580903) is investigating the use of infliximab in hospitalised patients with clinical features of COVID-19. This trial is recruiting in the United Kingdom (UK) where rates of hospitalisation are low and accrual rates are commensurately low. A pilot study in 17 patients is ongoing at Tufts Medical Centre (NCT04425538) and another pre-hospital study is planned to establish whether anti-TNF can prevent progression to severe illness. These trials

face significant recruitment challenges due to 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 to date means we need to continue the search for agents with greater efficacy. There is both biological plausibility and observational clinical data supporting the potential of anti-TNF as a treatment for COVID-19. Few current treatments under investigation have this level of support. There is a long history of safe use of anti-TNF in a diverse range of diseases and supply is plentiful with many originator products available as well as biosimilars. Anti-TNF therapy has now become a therapy with huge potential. We need to urgently investigate its value through prioritisation of clinical trial resources worldwide.

Conflicts:

PR reports personal fees from Abbvie, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Roche and UCB. Research grant funding from UCB, Janssen and Novartis. Non-financial support from BMS. All unrelated to this work.

DR reports personal fees for consultancy on drug safety from GlaxoSmithKline unrelated to the topic of this Comment.

HR reports no conflicts.

MF has 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.

References:

1. Recovery Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2021436
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2007764
3. Feldmann M, Maini RN, Woody JN, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet* 2020;395(10234):1407-9.
4. Del Valle DM, Kim-Schulze S, Hsin-Hui H, et al. An inflammatory cytokine signature helps predict COVID-19 severity and death. *medRxiv* 2020
<https://doi.org/10.1101/2020.05.28.20115758>
5. Charles P, Elliott MJ, Davis D, et al. Regulation of cytokines and acute phase proteins following TNFa blockade in rheumatoid arthritis. *J Immunol* 1999;163:1521-28.
6. Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* 1989;2(8657):244-247
7. Haworth C, Brennan FM, Chantry D, Turner M, Maini RN, Feldmann M. Expression of granulocyte-macrophage colony-stimulating factor in rheumatoid arthritis: regulation by tumor necrosis factor-alpha. *Eur J Immunol* 1991;21(10):2575-2579

8. Elliott MJ, Maini RN, Feldmann M, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum.* 1993;36(12):1681-1690
9. Ingegnoli F, Fantini F, Favalli E, et al. Inflammation and prothrombotic biomarkers in patients with rheumatoid arthritis: Effects of tumor necrosis factor-alpha blockade. *Journal of Autoimmunity* 2008;31(2):175-9.
10. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF Antagonists, are Associated with Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results from an International Registry. *Gastroenterology* 2020; <https://doi.org/10.1053/j.gastro.2020.05.032>
11. Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020;79(7):859-66.
12. Winthrop KL, Brunton AE, Beekman S, et al. SARS CoV-2 infection among patients using immunomodulatory therapies. *Ann Rheum Dis* 2020; <http://dx.doi.org/10.1136/annrheumdis-2020-218580>
13. Bezzio C, Manes G, Bini F, Pellegrini L, Saibeni S. Infliximab for severe ulcerative colitis and subsequent SARS-CoV-2 pneumonia: a stone for two birds. *Gut* 2020; doi:10.1136/gutjnl-2020-321760
14. Dolinger MT, Person H, Smith R, et al. Pediatric Crohn Disease and Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 Treated With Infliximab. *J Pediatr Gastroenterol Nutr* 2020;71(2):153-155.
15. Stallmach A, Kortgen A, Gonnert F, Coldewey SM, Reuken P, Bauer M. Infliximab against severe COVID-19-induced cytokine storm syndrome with organ

failure-a cautionary case series. *Crit Care* **24**, 444 (2020).

<https://doi.org/10.1186/s13054-020-03158-0>