Background to new treatments for COVID-19, including its chronicity, through altering elements of the cytokine storm

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Summary
Anti-tumour necrosis factor (TNF) biologicals, Dexamethasone and rIL-7 are of considerable interest in treating COVID-19 patients who are in danger of, or have become, seriously ill. Yet reducing sepsis mortality by lowering circulating levels of TNF lost favour when positive endpoints in earlier simplistic models could not be reproduced in well-conducted human trials. Newer information with anti-TNF biologicals has encouraged reintroducing this concept for treating COVID-19. Viral models have had encouraging outcomes, as have the effects of anti-TNF biologicals on community-acquired COVID-19 during their long-term use to treat chronic inflammatory states. The positive outcome of a large scale trial of dexamethasone, and its higher potency late in the disease, harmonises well with its capacity to enhance levels of IL-7Rα, the receptor for IL-7, a cytokine that enhances lymphocyte development and is increased during the cytokine storm. Lymphoid germinal centres required for antibody-based immunity can be harmed by TNF, and restored by reducing TNF. Thus the IL-7- enhancing activity of dexamethasone may explain its higher potency when lymphocytes are depleted later in the infection, while employing anti-TNF, for several reasons, is much more logical earlier in the infection. This implies dexamethasone could prove to be synergistic with rIL-7, currently being trialed as a COVID-19 therapeutic. The principles behind these COVID-19 therapies are consistent with the observed chronic hypoxia through reduced mitochondrial function, and also the increased severity of this disease in ApoE4-positive individuals. Many of the debilitating persistent aspects of this disease are predictably susceptible to treatment with perispinal etanercept, since they have cerebral origins.

KEYWORDS
anti-TNF biologicals, COVID-19 treatment, dexamethasone, IL-7

Abbreviations: AD, Alzheimer's disease; ARDS, adult respiratory distress syndrome; BCG, Bacille Calmette–Guérin; CRS, cytokine release syndrome; DAMP, danger-associated molecular patterns; IBD, inflammatory bowel disease; PAMP, pathogen-associated molecular patterns; TBI, traumatic brain disease; Tfh, cell follicular helper T cell; TLR, toll-like receptor; TNF, tumour necrosis factor.

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1 | A BACKGROUND TO THE TERM CYTOKINE STORM BEING APPLIED TO COVID-19

The innate immune system is orchestrated and mediated by cytokines, and provides the first line of defence against viruses. Excess levels of these cytokines also cause illness. Not surprisingly, therefore, the severe form of COVID-19 is often clinically described as the consequence of a cytokine storm. As reviewed in 2007, this term, then already in common parlance, is used to describe the distinctive severe illness that everyone has experienced at some time, and that can overwhelm patients in a number of acute conditions. The path to this logic can be traced from the argument that excess generation of certain soluble mediators, including tumour necrosis factor (TNF), then little-investigated and not yet termed cytokines, cause the pathophysiological changes recognised as malarial disease. In a blinded study, this condition has been shown to be clinically indistinguishable from influenza, implying the same fundamental mechanism as well as appearance. Of particular relevance to COVID-19, both malaria and influenza can exhibit adult respiratory distress syndrome and neurological manifestations.

The term cytokine storm was initially unrelated to pathogens, having been coined to describe the clinical consequences of the intense host response seen in graft versus host disease. Importantly, the storm concept has never been described in terms of a particular mix, or concentration, of cytokines. Previously this field, which includes understanding and using OKT3, a monoclonal antibody against the C3 receptor on T cells, had begun to refer to the phenomenon as the cytokine release syndrome (CRS). It has largely continued to do so. Meanwhile the cytokine storm terminology successfully migrated the cytokine release syndrome (CRS). It has largely continued to do so. Meanwhile the cytokine storm terminology successfully migrated from doing so through the cytokines they induce. Adult respiratory distress syndrome (ARDS) is not restricted to viral diseases, being a common element in severe high inflammatory cytokine environments, be they other infections states, such as falciparum malaria, or non-infectious, such as traumatic brain injury (TBI). Severe falciparum malaria and TBI also share renal insufficiency and disseminated intravascular coagulation, both of which are part of the excess cytokine literature, and seen in COVID-19. Hence the pathophysiology of this new coronavirus disease can be best understood, as can falciparum malaria and TBI, in terms of the excess cytokines the patient generates and releases, not by whether this happens in infectious, be it viral or protozoal, or non-infectious, disease states. Cytokine storms, however localised an event, are thus a very useful descriptors for understanding many conditions, including severe malaria, TBI, and COVID-19. These same cytokines, central to innate immunity, are also acknowledged to be the basis of the inflammatory processes on which current understanding of TBI and stroke rests.

The first time the term cytokine storm was applied to an infectious disease was to describe severe influenza, a condition often, as noted above, indistinguishable from malaria, and also from COVID-19. Another telling parallel between malaria and this coronavirus disease began by a virologist colleague, Jean-Louis Virelizier, suggesting we use Bacille Calmette–Guérin (BCG) in our investigation of the link between TNF and disease in the mid-1970s. We observed BCG pre-treatment strikingly protected mice against malaria. Over 40 years later, this principle proved to translate to a very large cross-sample of the children of sub-Saharan Africa, and quite recently to COVID-19. Klinger and co-workers demonstrated this to be a specific consequence of BCG vaccination, with neither measles nor rubella vaccination having any effect. A ‘trained immunity’ (their inverted commas), associated with epigenetic reprogramming in monocytes after BCG vaccination by Netea and co-workers in experimental yellow fever, proved to change these cell’s cytokine profile. This plausibly also applies to BCG and COVID-19. The various cytokines noted in a COVID-19 context in this review, including TNF, IL-1β, IL-6 and IL-7, have been reported to be components of the COVID-19 cytokine storm that happens early in the illness, when influenza-like changes, including respiratory distress, are present.

Increased sensitivity to excess innate immunity disease states in APOE4 individuals provides an additional source of evidence that the centrepiece of severe COVID-19 is indeed excess innate immunity. Goldstein and co-authors have recently proposed, through association with a strong innate immunity response, that the ApoE4 genotype of a variant of human apolipoprotein E (in practice E3/E4 or E4/E4), predicts the propensity to manifest rapid and severe COVID-19 illness. As Goldstein gave as an example, individuals of African descent may have twice the frequency of the ApoE4 allele (30–40%) compared to individuals of European and Asian descent. A month after Goldstein’s text appeared, data extracted from the UK Biobank demonstrated an association between ApoE4 alleles and COVID-19 severity independent of pre-existing dementia, cardiovascular disease and type-2 diabetes.

Why the severity of COVID-19 and the other pro-inflammatory cytokine-dependant conditions is worse in ApoE4-positive individuals was clarified by Gale and co-workers. These authors compared inflammatory cytokine production by ex vivo whole blood human leucocyte cultures from ApoE4-positive and ApoE4-negative individuals. When stimulated with various standard toll-like receptor (TLR) ligands, ApoE4-positive cultures generated significantly higher levels of the standard TLR-triggered cascades of these cytokines than did ApoE3 cultures. Moreover, intravenous injection of bacterial lipopolysaccharide, a TLR4 ligand that was the prototype TNF inducer, into volunteers from each group induced extremely higher levels of this cytokine, a major initiator of the inflammatory cytokine cascade, in the ApoE4-positive group. Notably, IL-6 levels were no different. Another obvious implication of this relationship between ApoE4 positivity and COVID-19 severity is its capacity to contribute to the unexpected clinical severity of this coronavirus disease in individual patients, derive from the density and complexity of the geographic distribution of this genotype across the world. This
imply a need to monitor ApoE4 individuals, from whatever ethnic background, for their degree of COVID-19 illness.

2 | SEVERE CYTOKINE STORMS HARM LYMPHOID GERMINAL CENTRES AND THUS ANTIBODY-BASED IMMUNITY

TNF is a pleiotropic cytokine with many essential physiological effects, as well as being pathophysiological when in excess. Normal function of the lymphoid germinal centres needs initial activation by TNF in order to properly generate T helper cells and thus antibody-producing B cells. The white pulp in the spleens of patients dying from malaria show a marked architectural disorganisation. It has recently been reported in malaria models that T follicular helper (Tfh) cell precursors in the spleen of P. berghei ANKA and P. chabaudi—infected mice are poorly differentiated during severe infections. This loss of Tfh cells, and thus of splenic germinal centre function that are necessary for Ab production and therefore malarial immunity, was restored by depleting excess TNF, a key cytokine involved in malarial disease severity, and interferon gamma.

These principles were broadened to encompass other parasitic, bacterial and viral diseases in 2019. More recently, Kaneko and co-workers extended this approach to examining autopsy-derived thoracic lymph nodes adjacent to inflamed COVID-19 lungs. As well as high local TNF production, they found, in parallel with the above mouse malaria studies, follicular helper T cell (in this case Bcl-6+ Tfh cell) depletion. Peripheral blood studies revealed loss of transitional and follicular B cells in severe disease. This is discussed in terms of explaining the usually poor, short-lived, antibody response in COVID-19. Thus early treatment of COVID-19 patients with an anti-TNF (Sections 2 and 3) is reasoned to be expected to improve the duration of antibody-based immunity, as well as, in the author’s view, act synergistically, as a therapeutic, with rIL-7 and dexamethasone (Sections 5 and 6).

3 | COVID-19 ONSET DURING LONG-TERM ANTI-TNF THERAPY FOR UNRELATED CONDITIONS

While unusual, this way of acquiring basic information about a new disease has the advantage of being about real diseases allowed to play out in full, in a clinical setting, by unbiased individuals. Such data are inevitably of less statistical value than random controlled trials for various reasons, including case selection, but post-hoc observations such as these have the advantage of not being susceptible to placebo effects.

Specific anti-TNF biologicals are successfully established systemic long-term treatments for certain non-infectious chronic inflammatory states. Most experience comes from rheumatoid arthritis (RA) but also from psoriasis and Crohn’s disease. Before considering how this therapy is helping us understand COVID-19, it warrants noting the precedent of lowered Alzheimer’s disease (AD) incidence under these same circumstances. This has often been reported in RA patients treated regularly with specific anti-TNF biologicals and indeed repeated by Pfizer (unpublished, https://www.washingtonpost.com/business/economy/pfzer-had-clues-its-blockbuster-drug-could-prevent-alzheimers-why-didnt-it-tell-the-world/2019/06/04/9092e08a-7a61-11e9-8bb7-0fc796cf2ec0_story.html). These observations, together with more direct sources of evidence, have moved opinion towards the inflammatory theory of AD pathogenesis.

An identical chance encounter with a second disease, through community acquisition, during long-term anti-TNF treatment for another, also applies to COVID-19. Given its continuing high incidence in many countries, this viral disease has inevitably been acquired in many patients who are receiving anti-cytokine biologicals regularly to treat the pre-existing non-infectious chronic inflammatory states noted in the previous paragraph. A similar pattern has emerged, with regular administration of specific anti-inflammatory biological therapies reported to minimise harm in COVID-19 as well as having the expected useful outcome in the disease for which it was prescribed. In addition to a number of striking case studies reported by clinicians with considerable COVID-19 experience, to date two impressive reports that have emerged from international registries of chronic inflammatory conditions deserve particular consideration. The first to appear in print, from the gastroenterology community, noted that the prevalence of severe and complicated cases of COVID-19 was lower in patients undergoing inflammatory bowel disease (IBD) treatment with anti-TNF. Indeed, up to the submission date of their article, only 15% (30 of 198) of IBD patients with COVID-19 being treated with anti-TNF needed hospitalisation, and 3% of them required intensive care unit ventilator use, or died. In contrast, those IBD patients not receiving anti-TNF were hospitalised for COVID-19 in 67% of cases, with 25% of these requiring intensive care unit ventilator use, or dying. The second such publication to appear is from the international rheumatology registry. Six hundred COVID-19 cases from 40 countries were included in the study, and nearly a half of them had been admitted, with a significant inverse association between anti-TNF treatment and hospitalisation being found. One of the authors of this report, a member of the registry steering committee, equated this to an adjusted 60% reduction in hospital admission (https://www.medscape.com/viewarticle/930913).

These observations also carry the important inference that infections with SARS-CoV-2 are not exacerbated in patient treated with an anti-TNF biological, or a functionally related agent specific for another inflammatory cytokine. A large database of RA patients regularly treated with anti-TNF biologicals compared to untreated controls has demonstrated the same principle for influenza, a disease with clear similarities to COVID-19. In contrast, for 20 years it has been accepted that this treatment exacerbates certain bacterial infections such as tuberculosis.
Intriguingly, 30 years ago an anti-TNF monoclonal antibody and corticosteroids had been used to counter CSR. Both of these therapeutic approaches are still of major interest in a COVID-19 context, as discussed in this Section and Section 5. The first of the specific biologicals to be patented and used clinically were those specific for TNF, the archetypal inflammatory cytokine. These agents spectacularly transformed the treatment of chronic inflammatory states such as RA, Crohn's disease and psoriasis. The wealth of clinical experience with specific anti-TNF biologicals, with many millions of patients now having been regularly treated, has generated a cumulative knowledge of their use that makes them the obvious choice for novel inflammatory applications, whether systemic, as above, or intra-cerebrally via the perispinal route. In almost all countries patents have expired, making biosimilars affordable for government health services facing a pandemic.

Well before the present emergency, the logical response to the release of excessive levels of any harmful cytokine was to use a specific monoclonal antibody to nip the illness in the bud. To this end, positive outcome studies of sepsis in mice and baboons in high impact factor journals were broadcast widely in the mid-1980s as having set sepsis treatment on the course all were hoping to attain. However, outcomes of the next decade's research strongly reversed this opinion. As summarised by Deitch in 1998, the further other researchers explored beyond the precise experimental details, tools, timings, durations, endpoints and so on used in the original Beutler and Tracey publications, the more outcomes worsened. What eventually caught everyone's attention was that the realities of infection-initiated serious sepsis were very different, particularly in an infectious disease setting, in both mice and people, from that created within the limits of the experimental settings used a decade earlier.

Even so, the current novel human coronavirus infection has reawakened interest in analysing this cytokine storm model of disease pathogenesis. In this context, it would be informative for the diseases caused by experimental infections of other respiratory viruses to run their full course while exposed to anti-TNF biologicals. This has been achieved in mice, about 20 years ago, obviously without COVID-19 in mind, and initially using respiratory syncytial virus. TNF depletion reduced pulmonary recruitment of inflammatory cells, cytokine production by T cells and the severity of illness without preventing viral clearance. Influenza infections have also been followed in mice while exposed to an anti-TNF, our group using gemfibrozil intraperitoneally daily for 7 days, from the 4th day of infection, and by another group who administered etanercept intranasally 2 h after infection. From a different starting point, these trials essentially ask the same question as does the act of recording outcomes when the onset of COVID-19 illness occurs during long-term anti-TNF therapy for unrelated conditions, as summarised in Section 3.

All three mouse viral disease regimens in the above paragraph significantly increased survival. Could there be something different about a severe illness caused by viruses? Or did these positive outcomes depend on these studies having been performed in mice? Or on treatment being given early? Prescott has recently drawn attention to the Third International Consensus of Sepsis, which defines sepsis as a life-threatening acute organ dysfunction secondary to infection. Thus COVID-19 can be reasoned to be, ultimately, a sepsis. Within this logic, these outcomes, albeit with different respiratory viruses, and in mice, are consistent with the case made for alleviating the severe illness of SARS with early etanercept. Sixteen years later the same case, in principle, has been made for treating COVID-19. At the time of writing at least two trials of specific anti-TNF biologicals, adalimumab (http://www.chictr.org.cn/showprojen.aspx?proj=49889) and infliximab (https://clinicaltrials.gov/ct2/show/NCT04425538), are planned or in progress (Figure 1) against the current pandemic virus. Large comprehensive studies that are consistent with this approach continue to appear in the literature. An additional plausible element, increased generation and activity of bradykinin, has recently appeared within the cytokine storm aspect of this disease. While each of these publications discusses potential specific therapy, it warrants noting that this bradykinin pathway is on record as being inhibited by the anti-TNF therapy discussed here.

A conceptually different anti-TNF, XPro1595 (Quellor), is a molecularly engineered variant of TNF that rapidly forms hetero-trimers with native TNF to give a complex termed a dominant negative inhibitor of TNF because it can no longer bind and signal via TNFR1 or TNFR2. Clinical experience with this agent is currently very limited. It differs from conventional anti-TNF biologicals in that it leaves intact the immune response that wards off bacterial pathogens. There is currently no evidence whether this effect extends to viral pathogens. Clearly, this TNF variant needs testing for SARS-CoV-2, although current evidence is consistent with COVID-19 waning rather than waxing during any long-term anti-TNF therapy. Moreover, conventional use of anti-TNF biologicals against RA is not associated with increased influenza incidence or complications. Nevertheless, provided its cost compares to anti-TNF biosimilars plus antibiotics, this inherent anti-bacterial advantage of XPro1595 could plausibly be useful for lowering the incidence of secondary bacterial pneumonias from ventilator use. In Sections 4 and 5, however, the case is made that anti-TNF agents may be less appropriate than dexamethasone and rIL-7 at this severe stage of the disease. Moreover, its molecular size and data from those developing this agent infer that, like etanercept, it will have very little access to the cerebrospinal fluid unless administered peripherally. As discussed in Section 8, this is a promising approach to treat certain persistent aspects of COVID-19.

The demand for a practical COVID-19 treatment has attracted various research groups with expertise in inflammatory cytokines other than TNF to become involved. Accordingly, a recombinant IL-1R antagonist Anakinra, and anti-IL-6R antagonist Tocilizumab are being investigated for this purpose. To date, the most impressive
published study reported a 45% reduction in hazard of death in an anti-IL-6R inhibitor observational study comparing a treated versus an untreated cohort. Unfortunately, the first two controlled trials using this inhibitor have, at the time of writing, not been successful. Even so, IL-1β and IL-6 are demonstrably downstream from TNF in the inflammatory cascade, so the effects of these cytokines can be expected to be inhibited by anti-TNFs acting upstream. Notably, this was documented for IL-6 in controlled patient data derived from the penicillin-induced Jarisch-Herxheimer reaction seen in Borrelia recurrentis disease treated with anti-TNF, as discussed above. For these reasons, this commentary is largely restricted to TNF, since IL-1R or IL-6R inhibitors will need to establish an advantage over anti-TNF biosimilars in function, price or availability to be widely used. The same applies to manipulating other components of the inflammatory cascade in COVID-19, and conceivably will be encouraged by early results from psoriasis patients developing this viral infection while being treated with agents such as an anti-interleukin-23 (IL-23) inhibitor.

It is plausible, however, that these anti-inflammatory cytokine approaches, while rational before and during the initial cytokine storm phase, may well become less relevant should the disease become more serious in the ensuing weeks, when lymphopenia may become evident, and needs to be taken into account. At this time the effects of interleukin-7 (IL-7), a cytokine present from the onset of early cytokine storm that precipitates lung injury, evidently becomes more influential in determining outcome should the disease continue to worsen. This is discussed in Section 6 of this Commentary.

5 | IMPLICATIONS OF THE PRELIMINARY REPORT OF THE OXFORD DEXAMETHASONE TRIAL

Corticosteroids have been used to understand and improve outcomes in CRS, the tissue transplantation version of a cytokine storm, for 30 years. This history, coupled with pro-inflammatory cytokine increases in COVID-19, made it inevitable that this principle soon would be tested clinically in this new coronavirus disease. In the event it has been done in a conceptually simple but very large scale randomised, controlled, open-label trial involving about 15% of the UK hospitalised COVID-19 patients, spread over 176 NHS hospitals and coordinated by the Nuffield Department of Population Health at the University of Oxford. Among other things, this led to impressive n values—2104 patients in the usual care plus dexamethasone group, and 4321 in the usual care only group. In brief, a dose of 6 mg dexamethasone was administered as soon as possible after admission daily for up to 10 days (fewer if discharged earlier), with a median of 6 days, and the endpoint was 28-day mortality. In summary, the authors report that all participants, grouped, gave significantly (p < 0.001) higher survival in the dexamethasone arm over usual care alone. Subgroup percentage differences are intriguing: a 20% lower 28-day mortality (p < 0.002) in those requiring oxygen but not invasive mechanical ventilation, and a 35% lower 28-day mortality (p < 0.001) in those receiving invasive mechanical ventilation from the beginning. The implication, as has been noted, is that this trial supports dexamethasone being most effective in the sickest patients, those with a severe enough hypoxaemia to require ventilation. A meta-analysis of trials from 12 countries, assembled by a WHO
working group, is in broad agreement. A possible explanation for this disease stage effect is, as discussed in the next Section, the relationship between dexamethasone and IL-7.

Since excess levels of inflammatory cytokines such as TNF are well recognised to cause this type of severe illness, and corticosteroids inhibit generation of these cytokines, it is plausible to consider whether this dexamethasone trial and the outcome of COVID-19 acquired during long-term anti-TNF therapy for unrelated conditions are two sides of the same coin. In other words, is the above Dexamethasone trial saving lives through reducing generation of TNF (and indirectly thus other cytokines), while data from the gastroenterologists and rheumatologists achieve the same end by neutralising excess TNF and therefore downstream cytokines? Obvious points for consideration include the timing of dexamethasone dosage and subsequent reduction of cytokines, not only of TNF, but of those downstream of it that also exhibit pro-inflammatory activity. IL-1β and IL-6 are the obvious examples. It would be informative if at least these three cytokines, and also anti-inflammatory cytokines such as IL-4 and IL-10) were routinely assayed to maximise our understanding of the optimal time to treat with anti-TNF biologicals and dexamethasone during the course of a COVID-19 infection, as is being done elsewhere.

An intriguing novel way of envisaging a role of treatment with dexamethasone in this new viral disease is through its interaction with IL-7 activity. This interaction appears to be the opposite of dexamethasone’s effect on the other pro-inflammatory cytokines. With this comes a novel plausible synergy, as discussed in the next Section.

6 | A THERAPY FOR COVID-19 BASED ON THE ROLE OF IL-7 IN LYMPHOID CELL DEVELOPMENT

Another characteristic of severely ill COVID-19 patients is their lymphopenia, implying the loss of the ability to generate a range of interleukins required to maintain whatever immunity had developed while the disease was acute and relatively mild. With this immunity gone, patients are liable to be overwhelmed by the virus. Historically, the anti-inflammatory action of dexamethasone depends on its capacity to suppress a wide range of pro-inflammatory cytokines, including TNF, IL-1β, IL-6 and IL-17. The activity of IL-7, the interleukin on which regeneration of lymphocyte germinal centres, and thus generation of antibody, T helper cells and killer T cell depend, would, in contrast, be expected to be increased through dexamethasone enhancing levels of IL-7Ra. (Figure 1). This could explain the best outcome in the present version of this dexamethasone trial text being observed in the more severely ill individuals by their dexamethasone-enhanced endogenous IL-7 activity reducing TNF-induced apoptosis of their lymphocytes. Effectively, therefore, increasing the activity of one component of the COVID-19 cytokine storm, IL-7, inhibits a harmful activity of another, TNF. It is therefore logical to supplement endogenous IL-7 levels in moderate to severe cases, as discussed below.

From the observations summarised in Section 3, and also the detailed longitudinal studies by Lucas and co-workers, who concluded that an early elevation in harmful cytokine levels was associated with worse outcomes with this disease, it seems that the earlier anti-TNF is given, the better. Notably, dexamethasone is reported to be less effective early in COVID-19, a time characterised by wide-ranging pro-inflammatory cytokine increases. These authors have generated impressively complex longitudinal analyses of cytokine clusters, which is consistent with much of the effectiveness of dexamethasone administered in the later stage of the illness being mediated by its capacity to enhance IL-7 activity rather than its ability to inhibit the other pro-inflammatory cytokines.

The cytokine IL-7 was defined in the late 1980s during work on the development of lymphoid lineage cells. Clearly, this activity could bestow rIL-7 with therapeutic applications. By 2011, over a dozen trials, on a range of conditions, were recruiting to test this approach. In 2010, rIL-7 showed promise in a mouse sepsis model at a time when traditional leads had failed, and in 2016, rIL-7 was shown to be highly effective in lowering mortality in Pseudomonas aeruginosa-induced sepsis and pneumonia (92% survival in rIL-7-treated mice vs. 56% survival in control mice). This treatment increased absolute numbers of immune effector cells in lung and spleen and ameliorated the sepsis-induced loss of lung innate lymphoid cells. In recent years, lymphocyte functional enhancements induced by rIL-7 in both sepsis and COVID-19 patients have evidently been promising enough for a Pharma press release of rIL-7 therapy for COVID-19 (Figure 1) having been designated by the NHS as an urgent priority, and announcing enrolment at 10 UK trial sites having begun in May 2020, with more sites in France and Belgium in June. In summary, dexamethasone and rIL-7 can be predicted to synergise, since dexamethasone, through its enhancing effects on IL-7Ra, would increase the effectiveness of therapeutic rIL-7.

7 | CONTRIBUTION OF MITOCHONDRIAL DYSFUNCTION TO THE HYPOXIA OF COVID-19, AND THUS THE OBSERVED MULTIPLE ORGAN FAILURE

Like SARS before it, COVID-19 is dominated by a severe acute respiratory failure, leading to an all-pervasive hypoxia because the lungs can no longer do what is expected of them. Indeed, measurably hypoxic COVID-19 patients, beyond the point where compensatory breathing activity would be expected, display remarkably less respiratory distress than their measurable degree of hypoxia would predict. This is proposed to have arisen by the harmful effects of the virus (or from our perspective the TNF the virus induces) on the respiratory centre in the brain stem, which monitors CO2 to adjust respiratory effort. The net result is often that the actual
degree of hypoxia is worse than can be deduced by simple observation. A further source of hypoxia can be predicted, from the literature, through the effects of high levels of TNF generated in severe COVID-19. This TNF triggers an additional avenue of hypoxia through causing mitochondrial dysfunction. It has been appreciated for some time that excess TNF uncouples respiration in isolated mitochondria.\(^{99}\) This mitochondrial dysfunction can mediate, for example, TNF-induced neurotoxicity.\(^{100}\) Moreover, hypoxia has been demonstrated to induce TNF.\(^{101}\) These two generators of hypoxia, combined, plausibly gives a significant contribution to the multiple organ failure, involving renal\(^{12}\) and cardiac\(^{102}\) function, seen in COVID-19. It could also lead to the distinctive failure to wean off mechanical ventilation in this condition. In summary, these observations indicate further hypoxia-based justifications for anti-TNF therapy in this condition. This is not to discount possible IL-1 and IL-6 involvement, albeit relevant literature is not common. In any event, as noted earlier, many specific anti-TNF biologicals, which, as noted earlier, can be expected to also lower IL-1 and IL-6, have reached the biosimilar stage of their development, making them less expensive.

8 | NEUROPHYSIOLOGICAL DYSFUNCTION IN COVID-19, AND ITS PERSISTENCE

COVID-19 is not only a pneumonia—albeit potentially severe—but a multi-system disorder. Neurological dysfunctions are often the most distressing of the organ failures. These complications were soon appreciated to often persist, and to have long-term health ramifications. The range of functional cerebral loss can be appreciated to often persist, and to have long duration. \(^{8}\) COVID-19 is not only a pneumonia—albeit potentially severe—but a systemic disorder. Neurological dysfunctions are often the most distressing of the organ failures. These complications were soon appreciated to often persist, and to have long-term health ramifications. The range of functional cerebral loss can be appreciated to often persist, and to have long duration.

What these diseases have in common, and all they needed to generate the same syndrome, is strong PAMP activity to produce similar cytokine production. Indeed, essentially the same syndrome was inadvertently generated when first testing rTNF as a possible treatment for tumour patients,\(^{6}\) as discussed several paragraphs ahead in this Section. The concept of a misdirected virus-induced immune response has been mentioned in the coronavirus literature,\(^{513}\) but with no reference to cytokines, nor to consequences for cerebral function, as summarised in the next paragraph.

There is much evidence that SARS-CoV-2 can enter the brain, and that, being a pathogen (i.e., possessing PAMPs activity), it can generate excess TNF and related cytokines. This gives the virus the capacity to be randomly, and indirectly, harmful in this organ, in which low levels of properly orchestrated TNF are essential for normal physiological function. TNF is a remarkably preserved pleiotropic cytokine. It is strikingly primitive: when human TNF is introduced into cells of reef corals it demonstrates shared function with this organism’s own TNF, even sharing its receptor.\(^{114}\) TNF, normally released in homeostatically controlled quantities from microglia, astrocytes and neurons, is involved in physiological neuronal activity and, as reviewed,\(^{115}\) plays a crucial role in regulating the strength of normal synaptic transmission. TNF, of itself rather than through the inflammatory cytokine cascade it can trigger, is also involved in modulating excitatory neurotransmission,\(^{116}\) trafficking AMPA receptors,\(^{117}\) homeostatic synaptic scaling,\(^{118}\) and long-term potentiation.\(^{119}\) It also maintains normal background levels of neurogenesis.\(^{120}\) Mitochondrial function depends on TNF,\(^{121}\) as does regulation of the neurotransmitter, orexin.\(^{122}\) Crucially, TNF also regulates neuronal type-1 inositol trisphosphate receptors, which are central to neuronal Ca\(^{2+}\) homeostasis, and thus the ionic signalling cascades on which normal function of these cells depends.\(^{123}\) As discussed at length elsewhere,\(^{124}\) excess TNF causes glutamate excitotoxicity and synaptic shutdown in chronic cerebral cytokine storms. This mechanism has recently been discussed in the context of West Nile Virus-induced neurological changes.\(^{125}\) Clearly, all these functions are susceptible to local levels of TNF being outside its required homeostatic range, and timing. The resultant distorted functional pattern can be expected to be randomly determined by where TNF increase and consequent pathological alteration in homeostasis happens to occur, from one hour to the next. Loss of executive function, memory and neurogenic pain, which is well known to be controlled by excess cerebral TNF,\(^{124,127}\) are examples. Compared to TNF, IL-1β and IL-6 appear as yet to be little studied in cerebral function. They do, however, share TNF’s activity to at least some degree in physiology and neuroinflammation.\(^{128,129}\)

Fatigue and irregular sleeping patterns are very common and disabling aspects of neurophysiological dysfunction in COVID-19. It
seems evident, from the literature, that these behavioural changes are orchestrated by chronic increases in brain TNF, whether induced by a PAMP, as in infectious diseases, or DAMPs in post-stroke or post-traumatic brain injury syndromes. Importantly, the most compelling experiment has already been done. The first trials in which rTNF was administered to tumour patients are reported to have frequently caused, in the course of 115 treatment in 50 patients, lethargy and fatigue so severe that discharge of the patient from hospital at the completion of therapy was precluded. As we have previously discussed, a mechanism for TNF-induced fatigue has been proposed by Cavadi and co-workers. These researchers reported that TNF suppresses the expression of the PAR bZip clock-controlled genes Dbp, Tef, Hlf, and the period genes Per1, Per2 and Per3, which are involved in controlling circadian rhythm. This, the authors reasoned, provided a causal link between TNF and the fatigue associated with infectious and autoimmune diseases. Case reports of successfully treating post-stroke fatigue with perispinally administered etanercept are published. Fatigue is yet to be a primary outcomes measure in a random controlled trial of post-stroke etanercept via this route of administration, which to date (see a Commentary has been limited to endpoints of limb mobility and alleviation of neurogenic pain.

The excess cerebral TNF explanation for the origins of cerebral symptoms seen in COVID-19 also allows their persistence beyond the acute phase to be rationalised. To do so requires appreciating that cerebral, but not systemic, TNF generation persists extremely well after a single intraperitoneal injection of bacterial lipopolysaccharide into mice. TNF levels are considerably lower than those in serum, but they remain at about 80% of their peak in the brain for at least 10 months, despite becoming non-detectable in serum within 6 h. This is consistent with data that, at least in mice, once microglia are activated the TNF they generate keeps them in this activated, TNF-generating, state for a considerable period. In other words, TNF acts as an autocrine mediator of microglial activation. Hence the central nervous system function is especially vulnerable to continuing pathological functional change when TNF is generated within the brain, from many cell types, particularly microglia and astrocytes. For reasons outlined in the previous paragraph this leads to loss of functional homeostasis in vulnerable sites such as synapses.

One predictable consequence of chronically increased brain TNF is the continuing loss of the subtle TNF homeostasis we all depend on for learning, memory, and normal behaviour, becoming disrupted in the chronic neurodegenerative states associated with excessive CNS TNF. Persistent aspects of COVID-19 include fatigue, cognition and memory failure, myalgia, dysgeusia, anosmia. Poor cognitive and memory function are often mentioned, along with ‘brain fog’. These changes are consistent with those recorded as having been ameliorated by perispinally administered etanercept in post-stroke syndromes.

This is not surprising, since apart from the sources of excess cerebral TNF in COVID-19, cerebral hypoxia is an obvious outcome of stroke caused by the TNF-induced disseminated coagulopathy noted in Section 1. Clearly, a trial of perispinal etanercept in patients with post-COVID-19 neurological changes is of interest. Other manifestation of random excessive cerebral TNF levels are likely to be observed in post-COVID-19 neuropsychiatric syndromes. These can begin during the acute phase, and often persist. As Troyer summarises, SARS and MERS present a similar picture. The neuropsychiatric literature has discussed a role for cerebral TNF in the pathogenesis of these conditions for some years.  

9 | SUMMARY OF EMERGING THERAPEUTIC DIRECTIONS COVERED IN THIS REVIEW

As the pandemic months pass, acquired experience summarises COVID-19 as a serious, highly variable and often extremely persistent disease. Optimal therapeutic approaches inevitably require pathogenesis to be understood, and the logic of the literature leads us to regard COVID-19 as one of the causes of severe sepsis in which long-term quality of life is of major concern. However, the models used 20 years ago to devise a sepsis therapy told us little of practical value. For example, 6 years ago a large multi-centre bacterial sepsis trial showed that their anti-TNF regimen dramatically decreased plasma TNF in patients in the severe state of bacterial sepsis. This did not, however, translate into clinical benefit, arguably because prior TNF had already triggered decisive changes. This trial outcome appears to have finally convinced many that treatment with anti-TNF is futile when bacterial sepsis has become severe, implying that it is probably too late to treat COVID-19 in this way once it too is at the same stage. As discussed in Section 4, administering anti-TNF to treat IBD and RA, COVID-19 onset during long-term anti-TNF therapy for two unrelated conditions, tantamount to administering it early in the course of COVID-19, was much more successful. Through its harmful effects on lymphocytes, an excessive early TNF response helps set the scene for a later extreme illness, as well as weaker and shorter antibody response. For this and other reasons, it is most logical to administer anti-TNF agents early in the cytokine storm.

Both dexamethasone and IL-7 are being studied, but not in conjunction, as yet. Should these two approaches prove to add to the body of useful knowledge in this field, they are likely to synergise. This is because dexamethasone enhances IL-7Rα, and thus enhances IL-7 activity. The combination of this glucocorticoid and supplemental IL-7 with the recombinant form of this cytokine can be argued to be the optimal approach at this stage. Indeed, this IL-7 activity-enhancing property may well be what makes dexamethasone most efficacious later in the more serious stage of the disease.

The ability to counter the persistence of the harmful effects of COVID-19 would be an important step forward for the patient, and society. As summarised in Section 8, many of these same changes are seen in post-stroke syndromes and are proving to be reversible, strikingly and for the long term, by injecting etanercept by a novel route (Figure 1), as described. A first random controlled trial has now been performed, as referenced in Section 8, but further trials are delayed by the present COVID circumstance. It is difficult to view this trial, plus the decades of off-label treatments accumulated beforehand, without appreciating the plausibility of this treatment in...
circumstances in which chronically enhanced cerebral TNF is randomly produced through PAMP and DAMP activity, such as in COVID-19.

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CONFLICT OF INTEREST
I have no interests to declare.

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