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Commentary

Tocilizumab versus the Covid19 tempest: All’s well that ends well or much ado about nothing?

Todd C. Lee 1, 2, 3,*, Guillaume Butler-Laporte 3, Zain Chagla 4, Emily G. McDonald 1, 2

1) Clinical Practice Assessment Unit, Department of Medicine, McGill University, Montréal, Canada
2) Division of General Internal Medicine, Department of Medicine, McGill University, Montréal, Canada
3) Division of Infectious Diseases, Department of Medicine, McGill University, Montréal, Canada
4) Division of Infectious Diseases, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Introduction

Nearly 9 months have passed since the first report of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially described as a mysterious respiratory illness [1] that has gone on to catch the world off-guard. Since then we have learned a great deal about coronavirus disease 2019 (COVID-19) and made important strides in patient care including pivoting away from pre-emptive intubation, which may have inflated early mortality [2]. However, many questions remain unanswered. Since the outset, a severe phenotype of the disease associated with elevated markers of inflammation and culminating in substantial lung injury and death has been recognized to develop in a subset of patients [3]. Studies of potential treatments aimed at prevention and treatment of this phenotype have focused on medications with antiviral, antithrombotic, and/or anti-inflammatory properties. One of these treatments, dexamethasone, has already demonstrated a mortality benefit in a large randomized controlled trial [4]. Analogies with cytokine storm, which may or may not be an apt comparison [5], have led to an interest in interleukin-6 (IL-6) inhibition as a therapeutic modality for severe COVID-19. Tocilizumab is a biological IL-6 inhibitor therapy that is used for the treatment of rheumatoid arthritis and giant cell arteritis. Several observational cohorts have explored the repurposing of tocilizumab for COVID-19 [6,7] and there are, at present, dozens of registered clinical trials involving tocilizumab or sarilumab.

Against this backdrop, in a recent issue of Clinical Microbiology and Infection, Rodriguez-Baño et al. [8] tackle the management of patients with an inflammatory presentation by providing observational data in support of tocilizumab for certain patients with COVID-19. The authors conducted a retrospective cohort study in patients admitted to 60 hospitals in Spain between 2 February and 31 March 2020. Individuals selected for inclusion in this analysis were clinically ill with both fever and oxygen requirements at study enrolment but without immediate need for mechanical ventilation. Most importantly, they selected patients with signs of a ‘hyper-inflammatory’ response, which the authors defined by presence of an elevation in ferritin, D-dimer and/or IL-6 levels. After adjustment for several potential confounders, using a variety of techniques, the authors found that the receipt of tocilizumab without corticosteroids was associated with reduced hazard for intubation or death. By contrast, neither steroid therapy alone nor in combination with tocilizumab was convincingly protective for either outcome. Of note, a second observational study from Spain [7] was subsequently published in Clinical Microbiology and Infection and reported a decreased risk of death when tocilizumab was given to patients with high levels of C-reactive protein (>150 mg/L).

Strengths and weaknesses

Rodriguez-Baño et al. appropriately adjusted for several co-morbidities and used propensity score methods [8]. Before propensity score matching, the treatment groups differed, with a higher prevalence of cardiac disease and severe renal insufficiency in the untreated group. Comparatively, the tocilizumab group had a longer median duration of illness and hospitalization before enrolment as well as lower adverse negative prognostic markers (ferritin and D-dimer). Even after propensity score matching, some of these imbalances persisted. The major challenge due to the study...
design is that we will never know with certainty why in some cases a given therapy was chosen over no therapy at all. This confounding by indication [9] is extremely difficult to eliminate. Likewise, it is hard to ascertain through observational data alone whether patients who received tocilizumab monotherapy were systematically treated differently from those who did not.

Additionally, the authors attempted to address immortal time bias by excluding primary outcomes and performing a sensitivity analysis with a time-dependent covariate. Yet, there is probably residual survivor bias, because the fundamental definition of day 0 did not correspond to the day of admission, rather to the day of symptoms (interquartile range (IQR) 8–13 days) versus 8 days for the untreated group (IQR 6–11 days) and a median of 3 days in hospital (IQR 1–5 days) compared with 1 day (IQR 0–4 days) for the untreated group. Both factors may have had a bearing on the likelihood of death over the subsequent 21 days.

Context with data from randomized controlled trials

One of the unexpected findings from this study was an observed lack of benefit from steroids in contrast to the RECOVERY randomized controlled trial results [4] or a recent meta-analysis of steroid trials in critically ill patients [10]. There are several ways this can be reconciled. Perhaps, as in the tale of Goldilocks, the ‘porridge was too hot’: many patients received ten times the dose of steroids used in the RECOVERY trial and <10% of the cohort was treated with dexamethasone. Although it is tantalizing to assume that the steroid effect is a class effect, dexamethasone may work differently with its lack of mineralocorticoid activity and longer half-life. Indeed, a recent randomized controlled trial of methylprednisolone at higher equivalent doses to RECOVERY’s dexamethasone failed to demonstrate a mortality benefit [11] and methylprednisolone appeared to have the least benefit in the meta-analysis [10]. Finally, the patients in the SAM-COVID–19 cohort differed from those in RECOVERY with a lower prevalence of heart and kidney disease and fewer mechanically ventilated patients (1%–3% versus 15%) who seem to benefit most from steroids. Finally, we must always consider the possibility of residual confounding by indication and/or other differences in the care received by the steroid group in the present trial.

It is also important to put this observational data in context with several industry-sponsored trials that have examined IL-6-inhibiting monoclonal antibodies with disappointing conclusions. The phase III COVACTA trial (NCT04317092) found that tocilizumab did not reduce mortality in hospitalized patients with severe COVID-19 pneumonia [12]. Similarly a large trial of sarilumab (NCT04315298) in severe and critical COVID-19 was stopped by the data safety monitoring board because of a lack of benefit and a potential signal for harm in non-ventilated patients [13] and a second international trial (NCT04327388) also failed to meet its primary or key secondary outcomes [14]. Whether or not a specific subgroup of patients with a hyperinflammatory response might benefit as proposed by the authors remains to be seen in future (ideally randomized) trials.

Implications

Early rapid mobilization of research efforts allowed the investigators to collect valuable data through an observational cohort study and important attempts were made to control for confounding by indication and survivor bias in the analyses. The authors appropriately conclude with a proposal to investigate the role of IL-6 inhibition as dexamethasone emerges as standard of care, and they caution against widespread use based on observational data alone. Reconciling their results with those from randomized control trials raises important questions about the causal effect of the hyperinflammatory response and its role in the development of severe COVID-19. Given the promising findings associated with the use of corticosteroids, we speculate whether a broader anti-inflammatory approach is the best option for most patients, whereas only a subset of patients might benefit from targeted anti-inflammatory management. We hope that trials like RECOVERY (www.recoverytrial.net) and REMAP-CAP (www.remapcap.org) will soon bring substantial clarity to the role, if any, that drugs like tocilizumab might play in combatting the worldwide COVID-19 tempest.

CRediT statement

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