Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Cytokine stimulus

IL-6 antagonists to replace systemic corticosteroids as the preferred anti-inflammatory therapy in patients with COVID-19?

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An earlier systematic review and meta-analysis on the efficacy of tocilizumab, an interleukin-6 (IL-6) antagonist, reported no mortality benefits in patients with coronavirus disease 2019 (COVID-19) due to the limited number of randomized trials available during literature screening [1]. However, we are delighted by the results of the prospective meta-analysis [2] by the World Health Organization's Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, which included a total of 27 randomized controlled trials and demonstrated a significant association between administration of IL-6 antagonists and lowered 28-day all-cause mortality, compared with usual care or placebo, in hospitalized patients with COVID-19 (pooled odds ratio = 0.86; 95% confidence interval 0.79–0.95). Furthermore, among patients not requiring invasive mechanical ventilation at randomization, the risk of progression to requiring invasive mechanical ventilation or extracorporeal membrane oxygenation or death within 28 days was significantly reduced with the administration of IL-6 antagonist (pooled odds ratio = 0.77; 95% confidence interval 0.70–0.85). Also, among patients not requiring kidney replacement therapy (KRT) at randomization, the administration of IL-6 antagonist significantly reduced the risk of progression to requiring KRT or death within 28 days (pooled odds ratio = 0.79; 95% confidence interval 0.71–0.88). These findings have once again expanded our arsenal of effective therapeutic options against COVID-19; prior to the publication of this prospective meta-analysis, we have only systemic corticosteroids as an established therapeutic option to reduce the risk of mortality in patients with COVID-19 [3]. Therefore, we believe that the implication from these latest findings is to determine the relative role of IL-6 antagonists and systematic corticosteroids in the treatment of patients with COVID-19.

The REACT working group has previously reported the prospective meta-analysis [4] of 7 randomized controlled trials which demonstrated a significant reduction of 28-day all-cause mortality with the use of systemic corticosteroids in critically ill patients with COVID-19, relative to non-use of systemic corticosteroids (pooled odds ratio = 0.66; 95% confidence interval 0.53–0.82). Despite their established mortality benefits, the use of systemic corticosteroids in patients with COVID-19 is not without harm; the notorious side effects of systemic corticosteroids include hyperglycemia, which could negate its mortality benefits since hyperglycemia itself has been associated with increased mortality in patients with COVID-19 [5]. This is indeed one of the reasons that the World Health Organization discouraged the use of systemic corticosteroids in patients with COVID-19 during the earlier days of the pandemic, prior to the release of findings of the RECOVERY trial which reported mortality benefit with dexamethasone. In addition, the use of systemic corticosteroids in patients with COVID-19 has been associated with the development of secondary fungal infections such as mucormycosis, which is an angioinvasive fungal infection due to fungi of the order

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Mucorales currently running rampant in few countries [6], as well as pulmonary aspergillosis [6] which may be challenging to treat, as the first-line treatment, voriconazole, may result in major drug-drug interactions, while the second-line treatment, amphotericin B, often complicates initiation or may even result in cessation of treatment due to renal insufficiency.

At least two ongoing clinical trials directly compare the efficacy of IL-6 antagonists with systemic corticosteroids (NCT04329650 and NCT04345445) in patients with COVID-19. While we wait for their findings, based on the prospective meta-analysis [2] by the REACT Working Group, IL-6 antagonists can be an adequate substitute for systemic corticosteroids in the population of patients with COVID-19 where systemic corticosteroids are deemed beneficial – patients who require baseline non-invasive respiratory support. It was reported in the prospective meta-analysis [2] that the use of IL-6 antagonists was significantly associated with lower 28-day mortality in the subgroup of patients who at baseline required low-flow oxygen (pooled odds ratio = 0.81; 95% confidence interval 0.67–0.98) or required non-invasive ventilation (pooled odds ratio = 0.83; 95% confidence interval 0.72–0.96), respectively. Nevertheless, the use of IL-6 antagonists (cost of the subcutaneous prefilled syringe of tocilizumab = USD 1291.24 per unit; cost of the subcutaneous prefilled syringe of sarilumab = USD 1924.69 per unit) can be associated with higher costs of treatment compared to the use of systemic corticosteroids. Therefore, priority can be given to the population at increased risk of sustaining corticosteroid-related side effects, i.e., patients with COVID-19 and concurrent diabetes, especially in settings with limited resources. In fact, these settings are most likely to misuse systemic corticosteroids, leading to the widespread occurrence of secondary fungal infections. Nevertheless, IL-6 antagonists may not be an adequate substitute for systemic corticosteroids in patients who require baseline invasive respiratory support, since this subgroup of patients had demonstrated no improvement in 28-day mortality with the use of IL-6 antagonists (pooled odds ratio = 0.95; 95% confidence interval 0.78–1.16) [2], while systemic corticosteroids significantly improved 28-day mortality in this subgroup of patients (pooled odds ratio = 0.69; 95% confidence interval 0.55–0.86).

We also acknowledge from the prospective meta-analysis [2] that the combination of IL-6 antagonists and systemic corticosteroids may have synergistic/additive effects as demonstrated by a significant reduction in 28-day mortality in the subgroup with corticosteroid use (pooled odds ratio = 0.75; 95% confidence interval 0.66–0.85) but not those without corticosteroid use (pooled odds ratio = 0.94; 95% confidence interval 0.75–1.18). Some researchers [7] recently raised their concerns that the use of dual immunomodulation with systemic corticosteroids and tocilizumab in patients with COVID-19 may delay viral clearance and allow severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to accrue genetic diversity. While the effects of the combination of IL-6 antagonists and systemic corticosteroids could outweigh the effects assumed by systemic corticosteroids alone, it is currently unclear if these mortality benefits extend to every patient with COVID-19 who received both the systemic corticosteroids and IL-6 antagonists [8]. Therefore, pending more evaluation, we believe that the concerns with regard to the dual immunomodulation facilitating viral genetic diversification are probably valid and should not be easily dismissed [6], especially when there was already emergence of variants of concern with higher transmissibility, which undermines the effectiveness of mass vaccination against SARS-CoV-2.

The most likely group of patients to benefit from co-administration of systemic corticosteroid and IL-6 antagonists should be those present with very high IL-6 production, where the high IL-6 concentration can be hardly inhibited by the use of IL-6 antagonists alone [9]. These patients would have a little reduction in serum C-reactive protein (CRP) level after initiation of IL-6 antagonists, which signifies the requirement for systemic corticosteroids [9]. Indeed, in the prospective meta-analysis [2], patients with CRP level ≥150 μg/mL did not benefit from the use of IL-6 antagonists (pooled odds ratio = 0.96; 95% confidence interval 0.83–1.11); hence, regular monitoring of CRP level upon initiation of IL-6 antagonist is recommended. Patients without satisfactory reduction in serum CRP level upon initiation of an IL-6 antagonist can then be co-administered a systemic corticosteroid. Eşkazan et al. [10] recently derived the "Cerrahpaşa-PREDICT score", which is a new clinical scoring system utilizing clinical and laboratory parameters that predicts the 28-day mortality of patients with COVID-19 receiving tocilizumab (positive predictive value of 94.5% and negative predictive value of 92.9%), and this scoring system could perhaps be investigated in larger-scale studies its potential to prospectively identify patients who would benefit from the combined use of IL-6 antagonists and systemic corticosteroids. This way, we could minimize the virological risks of dual immunomodulation. In patients who received systemic corticosteroids and IL-6 antagonists, concomitant administration of antiviral agents may also be warranted to facilitate viral clearance [11].

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CRediT authorship contribution statement

Chia Siang Kow: Conceptualization, Writing – original draft. **Abdullah Faiz Zaihan:** Data curation, Writing – review & editing. **Dinesh Sangarran Ramachandram:** Writing – review & editing. **Syed Shahzad Hasan:** Conceptualization, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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