EDITORIAL

The REMDACTA trial: do interleukin receptor antagonists provide additional benefit in COVID-19?

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Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients hospitalised with COVID-19 are at risk of clinical deterioration due to organ dysfunction [1], mostly commonly of the respiratory system, resulting in acute hypoxaemic respiratory failure. In COVID-19 patients, clinical deterioration due to worsening organ dysfunction increases the risk of adverse outcomes such as increased hospital length of stay and mortality. Worsening organ dysfunction is thought to occur secondary to either the harmful effects of the viral infection or the host immune responses or combinations thereof [2]. Thus, it is plausible that the addition of drugs targeting the host immune responses (such as interleukin-6 receptor antagonists like tocilizumab) to antiviral therapy could provide additional benefit over antiviral therapy alone in patients with COVID-19. This was the hypothesis tested in the REMDACTA trial by Rosas and colleagues [3].

The REMDACTA trial was a randomised double-blind placebo-controlled trial conducted in 53 centres in Brazil, Russia, Spain and the United States. The study population included hospitalised patients with proven SARS-CoV-2 infection, with radiological evidence of pneumonia and need for supplemental oxygen of at least 6L/min. Nearly 88% of the trial population received corticosteroids during the 28-day follow-up period. This trial used 2:1 randomisation, with 434 patients randomly assigned to the tocilizumab plus remdesivir and 215 to the placebo plus remdesivir. Thus, the usual care was representative of the

current clinical practice guidelines [4], with the exception of remdesevir. Randomisation was stratified by geographic region and by clinical status at screening. Patients in the intervention arm received at least one dose of tocilizumab. The primary outcome was time from randomisation to either hospital discharge or ready for discharge to day-28, analysed as time to event, stratified by country and by baseline 7-category clinical status ordinal scale. There was no difference in the primary outcome between the tocilizumab plus remdesivir and the placebo plus remdesivir groups (hazard ratio (HR) (95% confidence interval (CI)) 0.97 (0.78–1.19)). The corresponding proportion of patients being 66.1% ($n=286$) in the tocilizumab plus remdesivir group and 67.1% ($n=144$) in the placebo plus remdesivir group. The 28-day mortality was 18.1% in the tocilizumab plus remdesivir group and 19.5% in the placebo plus remdesivir group, with a HR (95% CI) of 0.95 (0.65–1.39). The incidence of infections was similar in the tocilizumab plus remdesivir group (30.5%; $n=131$) and in the placebo plus remdesivir group (33.3%; $n=71$). The trial concluded that tocilizumab did not provide additional benefit, over and above usual care, that included remdesivir and corticosteroids.

Recently, a prospective meta-analysis (PMA) of interleukin-6 antagonists, that included data from the REMDACTA trial, concluded that interleukin-6 receptor antagonists (tocilizumab and sarilumab) provide additional benefit compared to usual care (summary odds ratio (OR) for 28-day mortality, 0.86 (95% CI, 0.79–0.95); $P=0.003$ based on a fixed-effects meta-analysis)[5]. Aside from the arguments that in the PMA the summary OR for 28-day mortality was 0.89 (95% CI, 0.76–1.05; on a random-effect meta-analysis) and the differences in the tocilizumab treatment effects in the blinded versus open

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label trials (summary OR (95% CI) 0.81 (0.72, 0.9) versus 0.95 (0.72, 1.26) [5]), why are the conclusions of the REMDACTA trial on the additional benefit with tocilizumab different to the PMA? Of note, the OR (95% CI) for 28-day mortality of REMDACTA trial within the PMA was 0.91 (0.91 (0.60–1.39)) [5]. The fixed versus random effects debate is that in the fixed effect model we assume that there is one true effect size which is shared by all the included trials and in the random effects model we assume that the true effect could vary between the included trials. Accepting that the 95% CI will have driven how the studies are weighted and, therefore, sources of error, the similarities in the fixed and random effects point estimates observed in the PMA [5] makes a case to use interleukin-6 receptor antagonists. The blinding versus open label effects debate is that blinding of the participants, healthcare providers and/or outcome assessors will prevent systematic differences in care provided or how the outcomes are assessed. When mortality is used as an outcome, as was the case in the PMA [5], the blinding versus open label debate is less relevant [6].

The trial population of REMDACTA trial appears similar to the RECOVERY Trial that showed benefit with tocilizumab, with one key difference: RECOVERY trial eligibility criteria included C-reactive protein (CRP) values > 75 mg/L as a marker of inflammation [7]. This generates the argument that CRP levels may be a useful biomarker to select or stratify patients. However, there was no heterogeneity of treatment effect within CRP categories (i.e. there was no difference in treatment effect with increasing C-reactive protein as a surrogate for greater inflammation) in the PMA [5]. The implications here are either that inflammation may not a good discriminant marker for tocilizumab treatment effect or that CRP is not an ideal biomarker for such stratification. For example, in rheumatoid arthritis where there is most experience with these medications, drug levels and patients with low serum levels of intracellular adhesion molecule-1 (ICAM1) levels and high chemokine ligand 13 (CXCL13) levels showed the greatest response to tocilizumab [8]. Thus, the much pushed argument to measure IL-6 levels as a predictive biomarker for tocilizumab may well be ill founded. Of note, IL-6 levels in COVID-19 are lower than other critical illnesses such as sepsis [9].

Higher viral loads within the respiratory tract are seen in deteriorating and in critically ill COVID-19 patients [10, 11]. Presence of virus in the respiratory tract activates the immune system, particularly T cells. Activated T cells produce chemokines which attract monocytes and transform them into inflammatory macrophages within the lungs. Inflammatory macrophages generate chemokines that attract more T cells into the already inflamed lung parenchyma. This lymphocyte–macrophage inflammatory circuit continues until viral clearance and causes lung damage [12]. Circulating SARS-CoV-2 RNA is detected in blood in 20% of critically ill patients [13]. Both respiratory viral load and presence of viral RNA in blood is associated with increased risk of severe disease and adverse outcomes such as death [11]. Therefore, a combination of antiviral drug with an IL-6RA could accelerate viral clearance, whilst providing immunomodulation. In the REMDACTA trial, although eligibility criteria included a positive SARS-CoV-2 polymerase chain reaction test within 7 days of randomisation, viral load information is unavailable to explore the above hypothesis. However, the use of remdesivir as usual care [14] perhaps makes this line of reasoning less important. A related argument to consider here is that in patients who receive remdesivir and corticosteroids as cointerventions, there is limited additional benefit with tocilizumab. However, in the RECOVERY Trial that enrolled a similar target population, there was additional benefit with tocilizumab in those patients who got corticosteroids [7], a treatment effect that was replicated in critically ill patients [15] and in all illness severity states within the PMA [5].

The authors modified the primary outcome during the trial. At the start of the trial, the primary outcome was clinical status assessed on an ordinal scale at day-28 to time from randomisation, which was modified to either hospital discharge or ready for discharge to day-28. The *ready for discharge* is a more sensitive, and subjective outcome. As a double-blind trial, outcome ascertainment is unlikely to be biased, despite being subjective. However, a more sensitive outcome would be expected to increase the event rate, which leads us to discuss the sample size calculations in the trial. The authors were expecting 520 events and a 2.5 day shorter time to hospital discharge or ready for discharge to day-28, to achieve a treatment effect using Hazard Ratio of 1.3. Aside from expecting an optimistic treatment effect, they observed lesser primary outcome events ($n = 430$) than expected. In a fixed sample size frequentist design, this reduces the likelihood of a confirmatory result. Thus, whether the trial results would have been different with more outcome events is a valid critique.

In summary, REMDACTA trial did not show additional benefit with tocilizumab. The treatment effects observed in the trial was within the confidence interval reported in the PMA, that informed the World Health Organisation living guidelines to recommend interleukin-6 receptor antagonists in the management of COVID-19 patients.

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Author contributions

All authors developed the outline. MSH wrote the first draft. All authors contributed to the critical revision of the manuscript for important intellectual content.

Declarations

Conflicts of interest

KCT declares no competing interests. MS-H is on the Editorial Board for ICM, an investigator on the REMAP-CAP trial, led the WHO REACT PMA on IL-6 antagonists. YA is on the Editorial Board for ICM and is an investigator on the REMAP-CAP trial.

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