

To immunosuppress: whom, when and how? That is the question with COVID-19

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In *ARD*, Ramiro *et al* report a number of sophisticated primary and sensitivity analyses from an observational cohort study conducted in the Netherlands during the height of the COVID-19 ‘first wave’ in Europe.¹ After a difficult March 2019 of high hospitalisation and death rates with COVID-19, on 1 April their institution started a standard protocol of treating patients with COVID-19 with high-dose methylprednisolone for 5–7 days during which time individuals not showing clinical improvement were also given the interleukin 6 (IL-6) receptor-blocking agent tocilizumab. The authors of the present study observed outcomes with this strategy and retrospectively compared these outcomes with similarly ill patients with COVID-19 treated with standard of care within the month prior. This comparison group included no patients treated with either methylprednisolone or tocilizumab. Patients eligible for the study included those with hypoxia, evidence of COVID-19 pneumonia and an elevation of at least two of the following: high C-reactive protein (>100 mg/L), high serum ferritin (>900 µg/L at one occasion, or a twofold increase of the level at admission within 48 hours) and high D-dimer level (>1500 µg/L). It should be noted that only one patient enrolled into this interventional study was on mechanical ventilation at the time of enrolment. While the two cohorts appeared similar in levels of illness, slight differences in anticoagulation use between the two groups were observed and the authors could not control for other potential unmeasured confounders related to the two different

time periods (eg, changing practices in ventilation). The authors explicitly and elegantly discuss the potential for such unmeasured confounding, acknowledge the limitations of observational studies and conducted a number of sensitivity analyses to mitigate these concerns. All of their analyses suggest the same direction and magnitude of effect, namely that patients in the steroid with/without tocilizumab group fared better. They were less likely to die, less likely to progress to needing mechanical ventilation and their clinical status improved more quickly. This is in line with a number of other observational studies reporting ‘success’ with tocilizumab and/or steroids. But a deep dive into that literature is not necessarily pleasant, as the heterogeneity in methods and results will leave you with a sure case of the ‘bends’.

STEROID THERAPY IN VIRAL PNEUMONIA INCLUDING COVID-19

While the early observational data regarding patients on chronic steroids at the time of infection suggested high rates of severe outcomes^{2–5} and subsequent warnings from WHO regarding the risk of steroids,⁶ the use of higher dose steroids in such patients at baseline was likely a marker of more severe underlying diseases. It was hard to extrapolate these observations to the question of whether actually treating COVID-19 with steroids would be potentially beneficial or risky, and their use with COVID-19 has been controversial from the beginning. Prior to COVID-19, studies involving patients with the related coronavirus severe acute respiratory syndrome were mixed. Some studies suggested decreased viral clearance and increased mortality,⁷ while others showed benefit in oxygenation and survival.⁸ Studies in the related coronavirus Middle East respiratory syndrome suggested decreased viral clearance,⁹ and retrospectively the use of corticosteroids was associated with increased risk of mechanical ventilation. For unrelated viruses like influenza, most studies found associations between corticosteroid use and worse outcomes. One

large influenza study using propensity score analysis found methylprednisolone in doses similar to that in the present analysis (with exception of the 250 mg loading dose on day 1 in the Ramiro *et al*’s study) was associated with higher risks of intensive care unit (ICU) mortality.¹⁰ What nearly all of these studies have in common was that they were observational studies subject to a number of limitations. They were not uniform in their dosing nor their timing of steroid use. When taken as a whole, there is very little about this literature that would leave an investigator enthusiastic about using steroids, although the questions were lacking well-designed randomised controlled trials (RCT).

Enter COVID-19, and we are now asking the same steroid questions. An early observational report from China that used propensity methods to match steroid-treated COVID-19 cases to non-cases suggested non-significant trends towards worse outcomes among those using 40–50 mg of methylprednisolone per day compared with those not using steroids.¹¹ Conversely, a before-and-after analysis performed in France using 1 mg/kg methylprednisolone suggested a reduction in death and ICU admission in those using steroids, although similar to the Ramiro *et al*’s analysis, they could also not fully account for potential changes in anticoagulation or ventilator management (eg, proning) that likely occurred between the two time periods.¹² A number of other retrospective studies have since reported findings, several suggesting benefits with less risk of ICU admission or mechanical ventilation, but multiple other analyses suggesting similar or higher risks of death among steroid-treated individuals. These divergent outcomes are difficult to interpret, as are the heterogeneity in steroid doses (generally between 40 mg/day and 2 mg/kg) and background ‘anti-virals’ being used in these studies (although most of these background therapies have now proven to lack efficacy, despite early, sometimes encouraging observational/open-label studies^{13 14}). Clearly, steroid RCT data are needed to help sort out the efficacy of steroids and the best time to employ them during the course of illness.

ANTI-IL-6 THERAPY

A small open-label non-comparative study in China was the first to report the use of IL-6 blockade in this setting, in which 21 patients were treated.^{14 15} Other institutional-based cohorts with and without ‘control’ standard of care arms have been reported, generally with the

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conclusion that tocilizumab 'seemed to work' as inflammatory parameters improved and mortality seemed to be less than expected or in comparison to historical or standard of care comparison groups.^{16–18} A case-control study from Brooklyn, NY, compared 96 tocilizumab-treated patients with 97 controls, and demonstrated lower mortality among those who were non-intubated (although this was only among 11 patients), but not among those who were intubated.¹⁹ Contrary to this study, an institutional cohort at the University of Michigan of patients with COVID-19 on mechanical ventilation suggested a strong survivor benefit for those using tocilizumab, as mortality was nearly halved, despite an increase in secondary bacterial infections. This analysis used propensity scores and inverse probability of treatment weighting to create and analyse a comparison cohort similar to the one using tocilizumab.²⁰ Other positive observational experiences exist that showed improvement in tocilizumab-treated individuals compared with historical controls. These include a small cohort in France where the risk of mechanical ventilation was decreased by 33%, as well as a larger cohort in Italy, where similar declines in the risk of mechanical ventilation were observed, despite an increase in the risk of new severe infections (13% tocilizumab vs 4% controls^{21 22}). Another recent analysis, less sophisticated in its methodology but perhaps most pertinent to the Ramiro *et al*'s study, was a recent institutional observational cohort which compared mortality in those who used methylprednisolone and tocilizumab versus those who used tocilizumab without steroids, and found the combination to be superior to tocilizumab alone.²³ There are other observational studies with and without comparison groups to review, and most are heterogeneous in their methods and even in their results, but some, even using tocilizumab subcutaneously,²³ suggested enough benefit to justify studying IL-6 blockade more definitively in this setting.²⁴

CUE THE RCTS

In COVID-19, the standard of care has evolved very quickly, mainly regarding the use of anticoagulants (more and more used over time) and the use of mechanical ventilation (eg, given as late as possible over time, proning, and so on), both very important variables not adjusted for in any of the aforementioned trials using historical controls. Moreover, a potential concern regarding the Ramiro *et al*'s study

is the exceptionally high mortality rate (48%) in the historical control group, a percent that is higher than that observed in the control groups of most recent studies, particularly of non-mechanically ventilated individuals. This raises the question as to whether a historical control group, even one from several weeks earlier, is comparable given the rapid changes in care for such patients in the months of March and April of this year.

So, where are the RCT data? We are anxiously waiting as we try to make a coherent picture out of the haze of observational data. For steroids, an early glimpse has arrived. The UK Randomised Evaluation of COVID-19 Therapy (RECOVERY) platform demonstrating that dexamethasone given orally or intravenously at 6 mg/day for 10 days reduced 28-day mortality compared with usual care (mortality 21.6% vs 24.6%). This benefit occurred in patients receiving oxygen support (mortality 21.5% vs 25%), but mainly among those randomised while on mechanical ventilation (mortality 29.7% vs 40.7%). Interestingly, among those earlier in their disease course who were not receiving oxygen at the time of randomisation, a trend towards higher mortality was noted with dexamethasone (17% vs 13%^{25 26}). Until now, it is the only RCT having demonstrated a statistically significant survival benefit in patients with COVID-19.

So what about IL-6 inhibition? The preliminary results are not optimistic. Regeneron released a series of press releases with top-line results suggesting a lack of efficacy of their IL-6 receptor blocker sarilumab. Their phase 2/3 adaptive trial first reported that in phase 2, sarilumab was not effective in patients with less severe COVID-19 pneumonia (ie, those not mechanically ventilated²⁷). Subsequent study focused its primary analysis on patients who were mechanically ventilated at baseline in phase 3, and unfortunately, this trial failed to meet its primary endpoint of a 1 point improvement on the 7-point WHO ordinal scale. It is unknown whether additional analyses will find subgroups of individuals who benefited from this intervention, and it should be noted that the primary analyses focused only on a reported 194 individuals.²⁷ The separate global phase 3 Sanofi trial of sarilumab is still ongoing and results are not yet known. For tocilizumab, there exist several trials currently in France, the UK and Italy that have not yet published their data. Interestingly, the Italian study released a 23 July press release indicating that among 126 patients randomised to

tocilizumab or standard therapy, there was no difference in mortality; of note 28-day mortality was very low in both groups (3%) suggesting that included patients were not very severe.²⁸ While it is conceivable that tocilizumab and sarilumab studies could reach different conclusions, the mechanisms of the two drugs are identical (they both block membrane-bound and soluble IL-6 receptor) and they have been shown equivalent in efficacy and safety in rheumatoid arthritis.²⁹ Regardless, it is possible that differences in inclusion criteria, timing of dosing in relation to infection, background therapies, or differences in effective dosage could produce different conclusions when evaluating these two drugs. We anxiously await the conclusion of ongoing sarilumab and tocilizumab studies, as presently it is unclear who might benefit, and when, from IL-6 inhibition.

While open-label and non-randomised studies are hypothesis generating and can inform aspects of RCT design, we have learnt from hydroxychloroquine, chloroquine, ritonavir and others that early excitement may not portend success in the RCT setting. Ramiro *et al* should be commended, as they have perhaps conducted the closest analysis to an RCT as one could achieve in an observational setting. Their data certainly support the idea that current and future studies should evaluate the combination of methylprednisolone and tocilizumab. In general, COVID-19 trials have not been easy, the adaptive designs challenging, the pace frantic, the endpoints have changed over time and background therapies change by the month. It is an evolving science, and it is possible that RCTs even involving the same compound will produce heterogeneous or inconsistent results between studies. Steroids and IL-6 inhibitors likely 'hurt' if employed too early, and are likely ineffective if employed too late. Finding the sweet spot, if one exists, will require multiple trials. So put your mask on and wait. We should have answers soon.

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