RECOVERY trial investigators

27 November 2020

Dear Colleagues

Tocilizumab in the RECOVERY trial

Thank you very much indeed for your huge contribution to the RECOVERY trial. With your support, RECOVERY remains the largest trial of treatments in COVID-19, with nearly 19,000 participants to date. The clear results on dexamethasone, hydroxychloroquine, and lopinavir-ritonavir have changed the treatment of this disease worldwide, doubtless saving many thousands of lives. Over the next few months, we can expect to see equally convincing results about the effects of multiple other treatments being studied in RECOVERY, including azithromycin, convalescent plasma, and the REGEN-COV2 neutralising antibody combination.

As you know, RECOVERY includes a randomisation between tocilizumab and usual care alone for patients that have low oxygen saturations or need ventilation and have evidence of significant inflammation. At present, over 2000 participants have been randomly allocated to tocilizumab vs. usual care alone. We have sufficient tocilizumab supply to randomise a further 2000 participants in total.

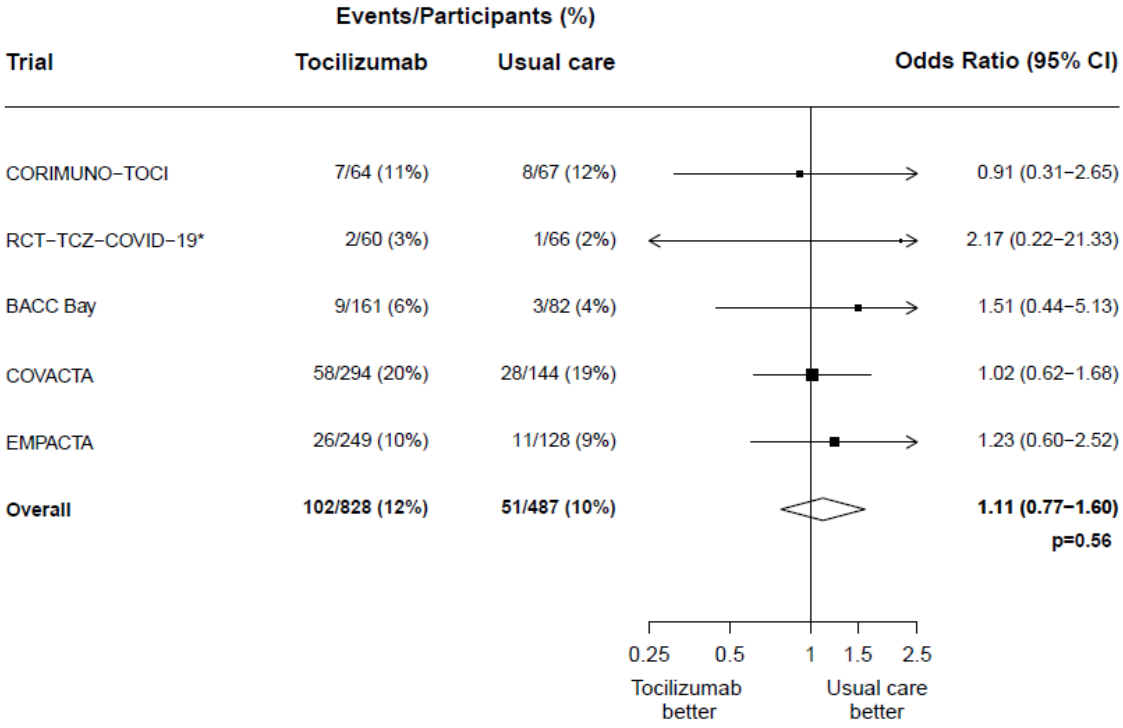
We are aware that a COVID-19 Therapeutic Alert regarding tocilizumab went out to all NHS hospitals yesterday. We have therefore summarised the information currently available on the effects of tocilizumab for COVID-19 and clarified the position with regards to enrolment of patients in RECOVERY.

REMAP-CAP: The REMAP-CAP trial (an international platform trial studying multiple treatments for COVID-19 in patients in intensive care) has been comparing the effects of tocilizumab (as well as other immunomodulatory agents) with usual care. Last week the investigators announced that on the advice of their Data Monitoring Committee they have discontinued recruiting to the usual care arm within that immunomodulatory domain because the data on 303 patients yielded '*an estimated odds ratio of 1.87 for a better outcome with tocilizumab compared to no immune modulation, with a high degree of statistical certainty (99.75% probability that tocilizumab is superior to no immune modulation).*'[1] No details are

[1] https://www.imperial.ac.uk/news/209033/arthritis-drug-effective-treating-sickest-covid-19/

available on the number of patients who died, the duration of ventilation, or the duration of hospital stay. Thus both the nature and size of the apparent benefit remain unknown both overall and in particular types of patients (for example those who may have been treated with corticosteroids). We all keenly await those details.

Published evidence: Five other randomised trials of tocilizumab have reported results to date, involving 1315 patients. As shown in the figure below, these have found no clear evidence of an effect on mortality. The effects of tocilizumab on other endpoints such as duration of hospital stay, need for invasive mechanical ventilation, and time to recovery are likewise inconclusive.



* RCT-TCZ-COVID-19 reported 30-day mortality.

Figure: Randomised trials of the effect of tocilizumab on 28-day all-cause mortality

RECOVERY: The independent Data Monitoring Committee met for its regular meeting on Thursday 19 November. The DMC reviewed the data on 1858 RECOVERY participants randomised to tocilizumab vs. usual care alone (of whom over 400 were known to have died) along with the available information from REMAP-CAP. The DMC recommended continuing recruitment of eligible patients to all active arms of the trial. The next routine meeting of the DMC is scheduled for Thursday 3 December.

IMPLICATIONS FOR RECOVERY: In the light of all the available information and the recommendation of the RECOVERY DMC (which was based on more patients and more study outcomes than all the previous trials put together), it is our opinion that there remains substantial uncertainty about the effect of tocilizumab in COVID-19.

Consequently, the randomised comparison of tocilizumab vs. usual care alone in the RECOVERY trial remains open. We encourage you and your colleagues to continue to enrol eligible patients.

The CAS alert from DHSC yesterday gives permission for tocilizumab to be used in patients who met the eligibility criteria for REMAP-CAP.[2] We have discussed this with Prof Chris Whitty (Chief Medical Officer for England) who has confirmed that this alert was permissive and not a directive or recommendation to treat patients with tocilizumab. The continuing enrolment of patients to the tocilizumab comparison in the RECOVERY trial has his full support.

We hope that tocilizumab will prove to be effective in COVID-19 but further data are needed before we can be confident of its safety and efficacy. We are very grateful for all your support in helping to provide such important data for the benefit of future patients.

Yours sincerely

Peter Horby PhD FRCP

Martin Landray PhD FRCP

Chief Investigators for the RECOVERY trial

[2] https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103116