Justification of substantial amendment for RECOVERY protocol V15.0

This document is a detailed justification for the changes to the RECOVERY protocol in version 15.0. The change number refers to the Amendment Tool change number included with this amendment.

Change 1: Addition of infliximab

Infliximab is an anti-tumour necrosis factor-α (TNF-α) monoclonal antibody. TNF-α plays an important role in inflammation, promoting the secretion of other pro-inflammatory cytokines, the recruitment of inflammatory cells, and cell death. TNF-α inhibition down regulates cytokines (IL-1, IL-6, IL-8, GM-CSF), acute phase proteins and coagulation biomarkers, and reduces neutrophil extracellular trap formation. Specific evidence for a causal role for TNF-α in COVID-19 has been demonstrated in vitro and in mouse models,[1] through gene expression profiling in lung tissue and blood from COVID-19 patients[2] and through the identification of high levels of TNF-α at hospital admission as an independent predictor of survival in COVID-19.[3] The UK COVID-19 Therapeutics Advisory Panel has recommended that infliximab be evaluated in patients hospitalised with COVID-19.

Infliximab has been licensed for over 20 years and is widely used for the treatment of rheumatoid arthritis, inflammatory bowel disease, and psoriasis. We therefore wish to include infliximab in the protocol, initially at the international RECOVERY sites where baricitinib is unavailable.

Given the low rate of admissions for COVID-19 in the UK currently (and the ongoing assessment of baricitinib) it has been decided to begin this assessment in countries outside the UK (which do not have any available IMPs in the protocol since the removal of colchicine and aspirin – see below). Should case numbers rise in the UK, then a further amendment would be submitted to begin this assessment in the UK as well. (This is also true for the high-dose corticosteroids [change 2].)

Dose selection

The selected dose is 5 mg/kg given as a single intravenous infusion in 250 mL 0.9% sodium chloride over 2 hours. This is the same dose given for inflammatory bowel disease, which in this context may be given every 8 weeks.

Participant population

It is possible that infliximab will have benefits across the disease spectrum. Therefore, adult hospitalised patients will be eligible as long as their responsible clinician does not consider treatment with infliximab to be absolutely indicated or absolutely contraindicated.

Infliximab has been widely used in inflammatory conditions in pregnancy, including rheumatological, gastroenterological, and dermatological autoimmune diseases. A systematic review of publications included 4276 cases who had received infliximab.[4] The review concluded that there was no signal of an increased risk of congenital malformations. Whilst an increase was noted in infections in children after pregnancy exposure to infliximab, this was based on retrospective recall, often in combination therapy with thiopurine treatment, typically with prolonged use (rather than a single dose as advised in the RECOVERY protocol). However, women should be advised that if treated after 20 weeks' gestation, their infant should not be immunised with live vaccines (rotavirus and BCG) for the first 6 months of life. All non-live vaccinations are safe and should be undertaken.

We do not plan to recruit children to this assessment.

Based on the mode of action there are no theoretical grounds to modify the dose in elderly patients, or those with renal or hepatic impairment.

Contraindications and cautions

Infliximab is associated with reactivation of tuberculosis. Patients with known active tuberculosis would be excluded from this comparison. In countries where TB is endemic, patients with previously incompletely treated TB or previous multidrug resistant TB would be excluded. In these countries, all participants would be provided with information about the potential for TB to develop and would be followed up at 3 and 6 months to check for TB (see "endemic infection" section of appendix 2 to the protocol).

Chronic administration of infliximab has also been associated with reactivation of hepatitis B, but there is no evidence that this occurs after a single dose. In parts of the world where hepatitis B is common (not including the UK), patients will be tested for and provided prophylaxis as described in the "endemic infection" section of appendix 2 to the protocol.

The summary of product characteristics contains advice about giving infliximab to patients with class III-IV heart failure. This concern follows a trial comparing 5 mg/kg, 10 mg/kg and placebo given three times over 6 weeks. The potential harm was only observed in the 10 mg/kg group, so this risk would seem unlikely to be relevant to a single dose of 5 mg/kg. Other risks described in the summary of product characteristics are relevant to chronic administration, but are very unlikely to occur with a single dose. Nevertheless, the low risk of such complications should be balanced against the considerable risk of death from COVID-19 among hospitalised patients (approximately 1 in 5 die), so any benefit from infliximab is likely to outweigh these risks.

All non-COVID infections will be captured on the study Follow-up form, following the introduction of these data to the protocol in version 14.0.

Change 2: Addition of high-dose corticosteroids

Favourable modulation of the immune response is considered one of the possible mechanisms by which corticosteroids might be beneficial in the treatment of severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS. Common to severe cases of these infections is the presence of hypercytokinemia and the development of acute lung injury or acute respiratory distress syndrome (ARDS).[5-8] Pathologically, diffuse alveolar damage is found in patients who die from these infections.[9] RECOVERY and other randomised trials have now demonstrated the benefit of corticosteroids in hypoxic COVID-19 patients.[10,11]

RECOVERY showed that a dose of 6mg dexamethasone once daily for ten days or until discharge (which ever happens earliest) provided a significant reduction in mortality. Combining the IL-6 inhibitor tocilizumab with low dose dexamethasone resulted in a further reduction in mortality. This raises the question whether simply increasing the dose of corticosteroid could confer a similar clinical benefit to that of adding tocilizumab, but at substantially lower cost. Of note, even with dexamethasone 6mg and tocilizumab, mortality remained high at 29%. Although other randomised clinical trials in critically ill COVID-19 patients have used higher doses of dexamethasone (20mg once daily for five days followed by 10mg once daily for a further five days) and reported clinical benefit, these doses have not been compared with the lower dose used in RECOVERY. There is, therefore, uncertainty regarding the optimal dose of corticosteroids in moderate to severe COVID-19.Uncertainty remains about whether higher doses of corticosteroids may provide additional benefit in adults with hypoxia hospitalised with COVID-19.

Unlike lower doses, higher doses (>15mg dexamethasone) would completely saturate cytosolic glucocorticoid receptors and have enhanced non-genomic effects.[12] In conditions where rapid control of inflammatory processes are required, short-term, high to very high doses of corticosteroids are used e.g.

- Sepsis 7.5 - 15mg dexamethasone equivalent daily[13]
- ARDS: 20mg dexamethasone for five days followed by 10mg for five days[14]
- Bacterial meningitis: 40mg dexamethasone daily for four days[15]
- Tuberculous Meningitis 0.4mg/k/day dexamethasone for 7 days then reducing over 8 weeks.[16]
- Rheumatoid arthritis flare: 120mg dexamethasone pulse therapy.[17]
- Community acquired pneumonia: 0.6mg/day dexamethasone for 2 days and methyl prednisolone 200m g /day then 80m g /day for 10 days.[18]

Dose selection

The selected dose is 20 mg dexamethasone given either orally or by intravenous injection once daily for 10 days (or until discharge, whichever is sooner). This dose is similar to other trials comparing high- and moderate-dose corticosteroids (NCT04636671, NCT04395105, NCT04726098). It would be expected that all participants in the usual care control group would receive 6 mg dexamethasone (or equivalent).

Participant population

This comparison would be restricted to patients requiring oxygen (including those on ventilation) at baseline, because RECOVERY has shown no benefit of treating patients not requiring oxygen with moderate dose steroids. We do not plan to recruit children to this assessment. Equivalent doses of oral prednisolone (130mg) or intravenous hydrocortisone (540mg) or methylprednisolone (100mg) would be used in pregnant women.

Contraindications and cautions

The side effect profile of high-dose corticosteroids are well-known and any patients considered unsuitable for such treatment (e.g. those with poorly controlled diabetes) would be excluded from the comparison by their doctors.The risk of endemic infections with high-dose corticosteroids has been considered, but no additional measures are considered necessary (see “endemic infection” section of appendix 2 to the protocol).

Change 3: Removing colchicine from the protocol

The Data Monitoring Committee recommended on 4 March 2021 that recruitment to the colchicine comparison be discontinued as there was no evidence of benefit either in the overall study population (11,340 participants) or any subgroup. Recruitment was therefore halted and follow-up is ongoing.

Change 4: Removing aspirin from the protocol

The Chief Investigators determined (after discussion with the Steering Committee) that sufficient participants should be recruited to the aspirin comparison to have good power to detect a 12.5% proportional reduction in the risk of death at 28 days. Recruitment was therefore stopped on 21 March 2021, but follow-up is ongoing.

Change 5: Updated Investigators’ Brochure for REGN-COV2

The Investigators' Brochure for REGN-COV2 was updated. The update does not change the Reference Safety Information nor the risk/benefit analysis of the treatment so did not require submission as a substantial amendment. It is included here for information.

References

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