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Antibody response to SARS-CoV-2 in patients receiving glucocorticoids with or without tocilizumab for COVID-19-associated hyperinflammation

Several immune mechanisms resembling a hyperinflammatory state have been critically involved in the pathophysiology of severe COVID-19, motivating the use of immunomodulatory therapies in the management of these patients. Various studies have already suggested the efficacy of immunomodulatory medication of treatment for severe COVID-19.¹⁻³ However, concerns have been raised about the impact of these therapies on immunity.^{4,5} We analysed the presence and levels of antibodies to SARS-CoV-2 in patients recovered from severe COVID-19-associated hyperinflammation after receiving no immunomodulatory therapy, and compared them to patients who received methylprednisolone alone or methylprednisolone followed by tocilizumab.

Between March and May 2020, 197 patients were diagnosed with COVID-19-associated hyperinflammation in the Zuyderland Medical Centre. In order to meet the criteria for hyperinflammation, patients had to fulfil specific characteristics that have been previously reported in this journal.¹

Up to the 1st of April, patients were treated with standard of care. In April and May, patients were treated according to the COVID-19 high-intensity immunosuppression in cytokine storm syndrome (CHIC) protocol with immunomodulatory therapies. This protocol included two steps: (1) high-dose intravenous methylprednisolone 250 mg on day 1, followed by methylprednisolone 80 mg intravenously on days 2-5, and an option for a 2-day extension; (2) in case of no recovery after 48 hours, escalation with tocilizumab (single-dose tocilizumab, 8 mg/kg body weight intravenous, max 800 mg).¹

Total antibodies to SARS-CoV-2 were measured in 117 recovered patients (79.5% male, median age 64 (SD 11.4) after a median of 3 months (IQR 1), 2 months (IQR 1) and 3 months (IQR 2) after onset of symptoms in the standard of care group, methylprednisolone group and in the methylprednisolone with tocilizumab group, respectively. Seventy patients died before follow-up.

Baseline demographic characteristics and clinical status during admission of three groups were similar (data not shown). Antibodies (IgG and IgM) to SARS-CoV-2 were measured using WANTAI SARS-CoV-2 Ab enzyme-linked immunosorbent assay (Wantai Biological Pharmacy, China). This test is considered negative if the WANTAI-Index is ≤ 0.9 and positive if the WANTAI-Index is ≥ 1.1 . A WANTAI-Index between 0.9 and 1.1 is considered borderline and retesting is required. The highest detectable WANTAI-index is 18. The sensitivity of this test is 95% and the specificity 100%.⁶

Neutralising antibodies were not measured.

The levels of antibodies were compared across groups with the Kruskal-Wallis test. The differences between groups of having a WANTAI-Index of 18 or < 18 were compared with the χ^2 test and logistic regression analyses were used to compute predicted probabilities thereof adjusted for potential confounders.

Median WANTAI-Index in all treatment groups was 18 (IQR 0). Antibody levels were not different across the three treatment groups ($p=0.486$).

Ninety-one percent (106/117) of patients had the highest detectable WANTAI-Index of 18. There were no differences

Table 1 Frequency of the highest titre of antibodies (WANTAI-index of 18) in 3 treatment groups (standard care/ no immunomodulatory therapy, methylprednisolone, methylprednisolone followed by tocilizumab), and predicted probabilities thereof adjusted for possible demographic and clinical confounders

	Standard care/ no immunomodulatory therapy (N=51)	Methylprednisolone (N=42)	Methylprednisolone and tocilizumab (N=24)	
WANTAI-Index of 18 (vs <18)	48 (94%)	37 (88%)	21 (88%)	p=0.517*
Predicted probability	94%	88%	88%	
Adjusted for age (years)	94%	87%	88%	
Adjusted for gender	85%	74%	89%	
Adjusted for BMI (kg/m ²)	94%	88%	87%	
Adjusted for smoking status	98%	95%	95%	
Adjusted for hypertension	94%	88%	88%	
Adjusted for diabetes mellitus	94%	87%	88%	
Adjusted for COPD	94%	88%	88%	
Adjusted for asthma	94%	87%	88%	
Adjusted for malignancy	94%	88%	88%	
Adjusted for haematologic malignancy	94%	89%	86%	
Adjusted for cardiovascular disease	94%	89%	87%	
Adjusted for heart failure	94%	88%	88%	
Adjusted for arrhythmia	94%	88%	88%	
Adjusted for chronic kidney disease	94%	87%	89%	
Adjusted for cerebrovascular disease	94%	87%	88%	
Adjusted for peripheral vascular disease	94%	85%	90%	
Adjusted for autoimmune disease	94%	88%	88%	
Adjusted for Charlson Comorbidity Index	94%	86%	88%	
Adjusted for WHO score baseline†	92%	86%	87%	
Adjusted for oxygen support at baseline†	94%	89%	87%	

WHO score, hospitalisation requiring oxygen or hospitalisation requiring high-flow nasal oxygen therapy or non-invasive ventilation or hospitalisation requiring extracorporeal membrane oxygenation, invasive mechanical ventilation or both; oxygen support at baseline, nasal oxygen or oxymask/non-rebreathing mask or high flow oxygen or mechanical ventilation.

*Calculated with Pearson χ^2 .

†Baseline is at the day that patients fulfilled the criteria for hyperinflammation.

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

across the treatment groups. Baseline characteristics did not influence the proportion of patients with the highest WANTAI-Index (table 1).

In 0.02% (2/117 patients) no antibodies were detected, one patient had received methylprednisolone and the other methylprednisolone plus tocilizumab. Interestingly, these two patients were being treated with rituximab for non-Hodgkin's lymphoma since before the diagnosis of COVID-19. None of the seropositive patients received monoclonal antibody therapy.

Based on these results, an effective long-term antibody response to SARS-CoV-2 infection does not seem to be impaired by immunomodulatory treatment of severe COVID-19 with hyperinflammation.

Our results may not be extrapolated to patients with milder forms of COVID-19 or patients already using (chronic) immunosuppressive agents for known underlying diseases.

In conclusion, a short-term therapy of COVID-19-associated hyperinflammation with glucocorticoids as well as with tocilizumab,

given in the first weeks of the disease, will not undermine the adaptive immune response in patients with COVID-19.

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