## Methylprednisolone as rescue therapy after tocilizumab failure in patients with severe COVID-19 pneumonia

Sirs,

Tocilizumab use in severe COVID-19 pneumonia is still controversial. One way to address its role is to assess possible rescue options after therapeutic failure. We aimed to describe, in an observational retrospective multicentric study, the impact of methylprednisolone as rescue therapy on hospitalised patients with COVID-19 pneumonia who did not clinically improve after receiving tocilizumab.

This is a secondary analysis preformed in consecutive patients from the TESEO cohort hospitalised from 1 March to 1 April 2020, who met the criteria for tocilizumab treatment failure (1). Tocilizumab failure in non-intensive care unit (ICU) setting, was defined per protocol as the lack of $PaO_2/FiO_2$ improvement after 72 hours from administration. Exclusion criteria were the use of glucocorticoids before tocilizumab. Two groups of patients failing tocilizumab were compared: the first group did not add any new immunomodulatory drugs, the second at the time of treatment failure, started methylprednisolone intravenously (1 mg/kg/day) for 5 days, tapering the dosage after 2 consecutive days of $PaO_2/FiO_2$ improvement.

The outcome of the study was death and/or IMV whichever occurred first during hospitalisation. The impact of methylprednisolone on outcome was assessed by a logistic regression model unadjusted and adjusted for age, sex, C-reactive protein (CRP) and Sequential Organ Failure Assessment (SOFA) score at hospital admission as potential confounders.

Of 60 patients, 26 (43.3%) received methylprednisolone. Table I describes the patient's baseline demographic and clinical characteristics. During hospitalisation, 12 (20.0%) patients reached the study end points: 2 (33%) underwent IMV but did not die, 5 (8.3%) underwent IMV and subsequently died, and 5 (8.3%) died without IMV (Table I). Among the 26 patients who received methylprednisolone, 9 (34.6%) had an outcome when compared to 3 (8.8%) in the group which did not. The unadjusted OR was 5.5 (95% CI=1.3–23.0, $p$=0.020). After adjustment for age, sex and SOFA score, OR was 2.45 (95% CI=0.46–12.95, $p$=0.291).

We described the impact of methylprednisolone as rescue therapy in hospitalised patients with COVID-19 who did not clinically improve after receiving tocilizumab. We depicted an initial harm signal of methylprednisolone associated with increased risk of death and IMV which was not confirmed after adjustment for age, sex, CRPand SOFA score.

Our study attempts to answer a relevant clinical question regarding the management of patients with clinically progressive severe COVID-19 that do not respond to tocilizumab treatment. In this setting, therapeutic approach are still not explored even as treatment strategies in the rheumatological field.

Our study was settled during the first wave of COVID-19 epidemic in Italy in which glucocorticoids were not recommended by WHO for the treatment of COVID-19, in consideration of the previous experiences from SARS and MERS (2).

The impact of the RECOVERY trial has rapidly changed the management of COVID-19 in different clinical settings. This trial promoted dexamethasone as initial treatment for hospitalised patients with COVID-19 pneumonia (3), but there is still a room for selective anti-cytokine therapies to be suggested as initial treatment.

Our observation investigated sequentially highly selective anti-cytokine drugs and broad-spectrum immune-active therapies, in patients with COVID-19 pneumonia with more severe clinical presentation. It may be hypothesised that tocilizumab may be ineffective in case of advanced cytokine storm or rather that higher dosage of methylprednisolone is needed to block at a multiple level the immunological cascades associated with MAS in people failing tocilizumab. In this setting, it may be attempted to use glucocorticoids at medium-high doses (prednisone 1 mg/kg/day or its equivalent) which is higher than what was used in the RECOVERY trial, or methylprednisolone pulses (500 to 1000 mg IV daily for 3–5 consecutive days) which was reported to be effective as initial monotherapy in patients with MAS and underlying systemic autoimmune diseases (4).

At present, the role of glucocorticoids as a rescue therapy after anti-cytokines monoclonal antibodies requires novel approaches to be evaluated in clinical trials.

**Table I.** Patients' characteristics.

| | | No methyl-prednisolone (n=34) | Methyl-prednisolone (n=26) | $p$-value |
|---|---|---|---|---|
| Age, years | median (IQR) | 62 (52-69) | 72 (56-80) | 0.0242 |
| Sex, male | n (%) | 28 (82.4%) | 16 (51.5%) | 0.1305 |
| SOFA score[1] | median (IQR) | 2 (2-3) | 3 (2-4) | 0.0057 |
| $PaO_2/FiO_2$[1], mmHg | median (IQR) | 227 (146-216) | 138 (103-170) | 0.0160 |
| Platelets[3], $10^9$/L | median (IQR) | 218 (194-239) | 221 (142-225) | 0.7184 |
| Total bilirubin[4], mg/dL | median (IQR) | 0.60 (0.52-0.72) | 0.67 (0.50-0.71) | 0.7860 |
| Creatinine[3], mg/dL | median (IQR) | 0.88 (0.70-0.93) | 0.92 (0.75-1.07) | 0.2232 |
| Haemoglobin[5], g/dL | median (IQR) | 13.7 (12.4-13.6) | 13.1 (12.2-12.9) | 0.0656 |
| Lymphocytes[6], $mm^3$ | median (IQR) | 1.0 (0.6 - 1.3) | 0.8 (0.6-1.2) | 0.4404 |
| C-reactive protein[1], mg/dL | median (IQR) | 14.1 (7.3-19.1) | 14.2 (7.6-17.9) | 0.9501 |

IQR: inter quartile range. [1]two missing values. [2]five missing values; [3]three missing values; [4]seven missing values; [5]seven missing values; [6]eleven missing values.

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**Data availability**

Derived data supporting the findings of this study are available from the corresponding author (GG) on request.

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