High dosage of methylprednisolone as a rescue, second-line treatment in COVID-19 patients who failed to respond to tocilizumab

We read with interest the article by Ramiro *et al*[1] about a cohort of patients affected by severe COVID-19 pneumonia. The authors evidenced the efficacy of 5 days of methylprednisolone (MP) (a single bolus of 250 mg, followed by 80 mg on days 2–5) plus, in case of insufficient response, tocilizumab (TCZ) 8 mg/kg, in reducing mortality and preventing invasive ventilation (IV).

As the massive lung damage during COVID-19 pneumonia is thought to be caused by an aberrant inflammatory response mediated by a massive release of inflammatory cytokines and chemokines, the use of biological immunosuppressants has been widely proposed. The rationale supporting their use is not only an antiviral effect,[2] but the selective anti-inflammatory role and the capability of interrupting the cytokine cascade eventually responsible for lung failure.

TCZ, a monoclonal antibody directed against interleukin 6 (IL-6) receptor, was the first biological drug administered in a Chinese cohort of patients. Despite preliminary promising data, recent reviews and meta-analysis did not find statistically significant differences, in terms of mortality, intensive care unit (ICU) admission and requiring of IV, between patients treated with TCZ and the control group.[3 4] Moreover, to our knowledge, no paper has evaluated the possibility of second-line treatment after a lack of response to TCZ.

We evaluated five patients affected by moderate to severe COVID-19 pneumonia, who failed to respond to azithromycin, hydroxychloroquine and two doses of TCZ. When admitted to the hospital, they all had chest X-rays evidence of bilateral interstitial pneumonia with diffuse consolidations. All patients had fever, cough and dyspnoea, while one reported also diarrhoea. Symptoms dated from 1 to 10 days before hospitalisation.

Blood examinations revealed elevated inflammatory markers, D-dimer, fibrinogen and ferritin and lymphopenia. All subjects required ventilatory support, ranging from venti-mask to IV.

In all five patients, hydroxychloroquine and azithromycin were immediately administered at diagnosis, whereas intravenous TCZ, 8 mg/kg, within 72 hours from hospitalisation, and then repeated after 24 hours. In two patients, TCZ was administered in ICU. None of them reported substantial benefit after anti-IL-6 treatment and one patient required ICU admission and IV.

From 3 to 5 days after the first administration of TCZ, all subjects were treated with intravenous MP 1.5 mg/kg, slowly tapered after 5 days. All five patients evidenced a prompt and remarkable improvement: within 7 days, all three subjects in ICU did not require IV anymore and were awakened (table 1).

Steroid therapy during acute respiratory distress syndrome (ARDS) is still a matter of debate, and the immunosuppressive effect often represents an obstacle for its administration in fragile patients. Nevertheless, a growing body of evidence supports its use in this condition, particularly in compromised patients.[5]

If the rationale of the use of TCZ and other biological drugs is the immunomodulation of the exaggerated immune response leading to ARDS, then glucocorticoids (GCs) s should not be rapidly neglected as an obsolete tool: immunosuppressive role of steroids is wide and embrace neutrophils, lymphocytes, macrophages and monocytes.[6] The aspects themselves which do not make GCs suitable for a chronic condition (lack of specificity, as well as the long-term side effects) may be the point of strength in such a hyperacute condition. As a matter of example, if a targeted and superselective action is the mainstay of the long-term treatment of any chronic inflammatory disease, no physician, in the clinical practice, treats a life-threatening condition with biological drugs only. Boluses of intravenous GCs and intra-articular injections are still recommended in case of severe autoimmune disease flares, as well as in many inflammatory conditions affecting upper and lower airways. In contrast, biological drugs, despite selective and with a good safety profile, have often a not negligible latency time.

Moreover, ARDS is mediated by a large number of ILs and growth factors: the selective inhibition of just one of them may be not sufficient to halt the cytokine cascade triggered by viral invasion. Finally, GCs raise concerns for their long-term administration, while their side effects are considerably minor in such a short treatment.

Our data, although limited by the small sample, confirm the evidence reported by Ramiro *et al*[1] about a possible synergic role of TCZ and MP in limiting the exaggerating autoimmune response leading to ARDS. The added value of our experience is that MP could be used also as a rescue therapy after TCZ administration and not only before. No significant differences emerge from Ramiro's shorter schedule, preceded by a small bolus, and ours, but we recommend an adequate dosage of GCs in order to fully take advantage of its action on nuclear gene transcription.

Table 1 Patients features

Males/Females	5/0
Mean age (SD)	54 (±6.69)
Comorbidities	Obesity (1),previous colorectal cancer (1), hemiplegia (1), none (2)
Mean P/F at TCZ administration	176.2 (±42.97)
Ventilation support at TCZ administration	VM (3), IV(2)
Mean P/F at MP administration	204.4 (±29.97)
Ventilation support at MP administration	IV (3), VM (2)
Mean P/F 7 days after MP administration	327.8 (±59.86) *
Ventilation support 7 days after MP administration	VM (4), AA (1)

*P<0.01.
AA, ambient air; IV, invasive ventilation; MP, methylprednisolone; P/F, PaO_2/FiO_2 ratio; TCZ, tocilizumab; VM, ventimask.

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Contributors EC wrote the article, BF supervised the work, BF, FF, SV and DB conceived the protocol scheme, EB, LV, SS, MAM.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Conticini E, Franchi F, Bennett D, *et al*. *Ann Rheum Dis* 2022;**81**:e202.

Received 31 July 2020
Accepted 2 August 2020
Published Online First 19 August 2020

► http://dx.doi.org/10.1136/annrheumdis-2020-218788

Ann Rheum Dis 2022;**81**:e202. doi:10.1136/annrheumdis-2020-218761

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