Therapy of Sars-Coronavirus-2 pneumonia: is there an optimal IL-6 cut-off for successful tocilizumab treatment?

Nicola Squillace*, Maria Rosa Pozzi ⁋ , Giulia Gustinetti*, Elena Ricci†, Serena Capici‡, Paola Columpsi*, Luca Sala‡, and Paolo Bonfanti*,

* Infectious Diseases Unit, Azienda Socio Sanitaria Territoriale di Monza,

"San Gerardo" Hospital, University Milano-Bicocca, Monza, ITALY

⁋ Rheunatology Unit , Azienda Socio Sanitaria Territoriale di Monza , Ospedale San Gerardo, Monza, ITALY

†Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, ITALY

‡ Phase 1 research centre, Azienda Socio Sanitaria Territoriale di Monza, Ospedale San Gerardo, Monza, Italy

Corresponding author:

Nicola Squillace, MD

Infectious Diseases Unit, Azienda Socio Sanitaria Territoriale di MONZA,

"San Gerardo" Hospital, University Milano-Bicocca

Via Pergolesi 33,

20900 Monza, Italy

Tel: +39 039 233 9588

Fax: +39 039 233 9327;

email address : nicolasquillace74@gmail.com

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Dear Editor,

Jordan SC et al. showed that the use of tocilizumab in 27 patients with severe Sars-Coronavirus-2 (SARS-COV-2) pneumonia was associated with reduced inflammation and risk of mechanical ventilation or death[1]. The mean IL-6 level at baseline was 356 ± 616 pg/ml[1]. Few studies evaluated prognostic value of IL-6 at baseline to predict clinical benefit of tocilizumab treatment.

Luo et al. described 15 patients (median age 73 years), with a median baseline IL-6 of 46.8 (range 16.4-627.1) pg/mL; 53% of patients received concomitant steroid therapy[2]. Death rate was 40% (most patients were critically ill at baseline) and no data were available about discharge of patients.

A recent meta-analysis evaluated 7 studies with available IL-6 levels and relative outcomes. In severe disease IL-6 levels were significantly higher than in non-severe and increasing mean IL-6 on admission was associated with increased likelihood of mortality, using meta-regression analysis[3].

Thus, although IL-6 inhibitors have a strong effect on inflammation, timing of use and IL-6 level at first administration can be crucial for therapeutic efficacy.

In our hospital, 32 consecutive patients with severe SARS-COV-2 pneumonia were treated with tocilizumab: 16 patients recovered, 6 patients died, 10 had a prolonged hospitalization (Patients' characteristics according to outcome are shown in the Table 1).

We compared 16 patients who were discharged within 30 days from first tocilizumab dose (group A) vs 16 patients who had prolonged hospitalization or died within 30 days from first tocilizumab administration (group B).

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A significant difference was observed in baseline IL-6 level: median was 77.3 pg/mL (IQR 60.7-143.1) in group A and 260 pg/mL (136.1-371.6) in group B (Mann Whitney U test p=0.0005). A significant difference was still observed at 24 hours post tocilizumab infusion: 759.8 (IQR 416.3-1273.0) pg/mL and 2551 (1132.0-4891.0) pg/mL respectively, (Mann Whitney U test p=0.003).

As regards days from symptoms onset to tocilizumab treatment, no significant difference was observed between the two groups (see Table 1), suggesting that inflammation level was more crucial than timing of treatment. Then, we used the median value of the whole sample (135 pg/mL) to define two level of IL-6 exposure: in group A 4/16 (25.0%) patients had IL-6 >median pg/ml, while in group B 12/16 (75.0%) patients had IL-6 >median pg/ml at baseline (Fisher exact test p=0.02) suggesting that IL-6 values >135 pg/ml were associated with adverse clinical outcome, as described in literature[3].

The very high level of IL-6 observed in patients with worst outcome could show an high burden of inflammation, not sufficiently inhibited by receptor blockade. We can speculate that a single dose of tocilizumab cannot efficiently suppress the pro-inflammatory activities of IL-6 trans-signaling because not only the IL-6 concentration is very high, but also IL-6R shedding at site of inflammation is increased[4].

The findings of our study suggest that tocilizumab could be more useful when IL-6 serum level is less than 135 pg/ml. It could be interesting to know if Jordan SC et al.[1] found a similar association with IL-6 at baseline and clinical response rate.

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Potential conflicts:

Dr. Squillace has consulted for ViiV Healthcare and received travel grants from Gilead Science, outside the submitted work; Dr. Bonfanti reports personal fees from Viiv Healthcare, Jannsen, Gilead Science, Merck, and Roche, outside the submitted work; and Dr. Ricci has received personal fees from Viiv Healthcare, outside the submitted work. All other authors have no potential conflicts to disclose.

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Table 1. Patients' characteristics according to clinical outcome.

Variables	Group A N=16	Group B N=16	p
Age, years, median (IQR)	66 (54.5-72.0)	63 (57.5-69.5)	0.69
Male sex, N (%)	12 (75.0%)	13 (81.3%)	1.0
BMI, Kg/m^2, median (IQR)	26.9 (25.1-29-9)	27.1 (24.8-29.9)	0.89
Time from symptoms onset to first tocilizumab dose, days, median (IQR)	13.5 (10.5-17.0)	13.5 (10.5-15.5)	0.52
IL-6 BL, pg/mL, median (IQR)	77.3 (60.7-143.1)	260 (136.1-371.6)	0.0005
IL-6 24h, pg/mL, median (IQR)	759.8 (416.3-1273.0)	2551 (1132.0-4891.0)	0.003
Ordinal scale 4 (non-invasive ventilation) at BL, N (%)	12 (75.0%)	13 (81.2%)	0.14
Steroid use, N (%)	6 (37.0%)	7 (43.0%)	1.0
Hypertension, N (%)	10 (62.5%)	9 (56.3%)	1.0
Diabetes, N (%)	0	3 (18.8%)	0.22
Ischemic heart disease, N (%)	0	2 (12.5%)	0.48

Group A: recovered; Group B: prolonged hospitalization or death. BMI, Body Mass Index; IL-6, interleukin-6; BL, Baseline; 24h, 24 h after first tocilizumab dose.