More evidences on which biologic and which pathway is key in severe-critical COVID-19 pneumonia

I read with great interest the paper by Della Torre *et al* on the effects of sarilumab in severe acute respiratory syndrome coronavirus 2 severe-critical pneumonia. They show that sarilumab treated and standard of care (SOC) treated patients present a mortality rate which is statistically not different (n 28 SARI=7% vs n 28 SOC=18%; p=NS).[1] These data confirm previous data from the same group; when analysing patients treated with tocilizumab, they showed no statistically significant differences (n 33 SOC=33%, mortality vs tocilizumab (TOCI) n 32=16%, p=NS).[2] These data seem to suggest that interleukin (IL)-6 is not the main target. Indeed out of more than 20 studies reported so far in the literature, only half reported clinically significant results (paper submitted). The various studies have so many bias and differences that a definite conclusion is impossible. However, since the approach with biologics has a strong rationale in controlling the cytokine release syndromes in the severe-critical phases of the disease and data on bronchoalveolar lavage cells, and on single-cell analysis suggest that some targets (IL-6, IL-8, interferon γ (IFNγ), Il1β, IFNα/β) are certainly more expressed than others,[3] it is and will be of crucial importance the definition of a possible hierarchy in the intervention, especially because targeting one molecule, and less others, may lead to control several other manifestations of the disease, such as the increased coagulation abnormalities[4 5] and the cardiac ECG abnormalities present in several of these patients.[6] The issue is then of clear biological but also of clinical relevance.[7] The San Raffaele group published two other important studies with different biologics, anakinra and mavrilimumab in severe-critical patients. In these two studies, the results were more favourable. In the anakinra (targeting IL1) study, they showed that the death rate with the SOC (n 16 patients) was 44% versus 10%, in the anakinra treated (high dose), p=0.009.[8] In the mavrilimumab (targeting granulocyte macrophage- colony stimulating factor receptor (GM-CSF-R)) study, they had a mortality rate of 26% (n 26 SOC), versus 0% in the mavrilimumab (MAVRI) (n 13) subset (Fisher's exact test=0.08).[9] All the studies had a 28-day follow-up as a censor-day time (table 1).

It is clear that the numbers are low and bias are high, yet they are hypothesis generating. However, the observation that different mortality rates are seen in the SOC groups (pretty similar in numbers) can be explained only if the patients are different. Given that they are different, could the AA provide a comparison of the entire cohort of SOC-treated patients (n 103) versus each single biologic to understand whether they show differences in terms of major outcome and how much is the difference considering the various biologics tested against the whole SOC cohort? The other possible alternatives, that is, that the 33 SOC patients in the TOCI trials represent the whole cohort, would be hard to understand because of the higher mortality rate, and the other possibility that some patients belong to one study and other patients to the other study again would raise the need to really understand which is the number of the overall cohort of SOC and the mortality rate in the SOC cohort. The analysis of the entire data set of patients treated with the SOC raises other possible bias, when making comparisons, yet it could offer the opportunity to better interpret the real value efficacy of each single biologic targeting different pathways.

Table 1 Major outcome with the various biologics in severe-critical acute respiratory syndrome coronavirus 2 pneumonia in the San Raffaele studies

Authors biologics	N of SOC treated patients	Death rate (%)	N of biologic treated patients	Death rate (%)	P value
Della Torre *et al*[1] *Sarilumab*	28	18	28	7	NS
Campochiaro *et al*[2] *Tocilizumab*	33	33	32	16	NS
Cavalli *et al*[8] *Anakinra*	16	44	29 (high dose)	10	0.009
De Luca *et al*[9] *Mavrilimumab*	26	27	13	0	Fisher's exact t =0.08

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Contributors GF: substantial contribution to study conception and design; substantial contribution to analysis and interpretation of data; drafted the paper for its intellectual content; finally approved the version fo the submitted article.

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 not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Ferraccioli G. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-218523

Received 9 July 2020
Accepted 10 July 2020

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-218612

Ann Rheum Dis 2020;**0**:1–2. doi:10.1136/annrheumdis-2020-218523

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