

THE LANCET

Rheumatology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
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Supplement to: Cavalli G, Larcher A, Tomelleri A, et al. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. *Lancet Rheumatol* 2021; published online Feb 4. [https://doi.org/10.1016/S2665-9913\(21\)00012-6](https://doi.org/10.1016/S2665-9913(21)00012-6).

Supplementary appendix

Pharmacologic treatment protocol

Antiviral therapy

For every patient unless specific contraindications:

- Hydroxychloroquine 200 mg BD orally
- Lopinavir/Ritonavir 400/100 mg BD orally

For selected patients with severe disease (in the ICU):

- Remdesivir 200 mg daily i.v. on day 1, then 100 mg i.v. daily until day 10-14 as compassionate therapy

Antibiotic coverage

All patients received an initial empiric antibiotic coverage for community acquired/hospital acquired pneumonia.

For patients admitted from home, without previous antibiotic exposure:

- Ceftriaxone 2 g i.v. daily
- Azithromycin 500 mg i.v. daily until negativization of urine antigen for *L. pneumophila*

For patients with negative cultures and decreasing inflammatory markers ceftriaxone was discontinued after 6 days of therapy.

In case of persistently high/raising inflammatory markers (especially procalcitonin), upgrade therapy to piperacillin/tazobactam + linezolid or meropenem alone was considered. For patients with previous antibiotic coverage or admitted from other healthcare institutions, initial empirical antibiotic coverage was decided on an individual basis depending on previous antibiotic exposure and risk factors for specific pathogens.

Baseline features

Cardiovascular disease.

Previous diagnosis of ischemic heart disease or congestive heart failure.

Diabetes.

Previous diagnosis of type 1 or type 2 diabetes mellitus according to International Diagnostic Criteria [1].

History of neoplasia.

Previous diagnosis of haematological or non-haematological malignancies, except for non-melanoma skin cancer.

- [1] Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020,” *Diabetes care*. 2020.

Supplementary Table 1 - Treatment characteristics (glucocorticoids) of 392 COVID-19 patients with respiratory failure and hyperinflammation.

Variable	Overall population (n = 392)	No IL inhibitors (n = 275; 70%)	IL-1 inhibitors (n = 62; 16%)	IL-6 inhibitors (n = 55; 14%)
Treatment with glucocorticoids				
No	325 (83)	221 (80)	55 (89)	49 (89)
Yes	67 (17)	54 (20)	7 (11)	6 (11)
*Cumulative mPDN-equivalent dose (mg/kg)				
Median	440	459	160	427
IQR	300 - 665	316 - 684	118 - 410	374 - 530
*Cumulative mPDN-equivalent dose (mg/Kg/day)				
Median	47	51	27	53
IQR	30 - 60	36 - 60	21 - 35	32 - 59
ICU admission				
No	360 (92)	263 (96)	49 (79)	48 (87)
Yes	32 (8)	12 (4)	13 (21)	7 (13)

*Estimated among patients receiving treatment with glucocorticoids.

Data presented as median and interquartile range or frequencies and proportions.

ICU: intensive care unit; IL: interleukin; IQR: interquartile range; mPDN, methylprednisolone

Supplementary Table 2 - Comparison of baseline descriptive characteristics of patients diagnosed with COVID-19 and hyperinflammation who did not receive IL inhibitors vs. patients treated with IL-1 inhibitors.

Variable	No IL inhibitors (n = 275)	IL-1 inhibitors (n = 62)	P value
Age (years)			0.003
Median	68	63	
IQR	58 - 79	52 - 73	
Gender			0.1
Male	201 (73)	52 (84)	
Female	74 (27)	10 (16)	
C-reactive protein (mg/L)			0.1
Median	127	143	
IQR	91 - 169	105 - 172	
*Ferritin (ng/mL)			0.08
Median	1239	1459	
IQR	841 - 1887	946 - 2761	
Lymphocytes (10⁹/L)			0.09
Median	0.9	0.9	
IQR	0.6 - 1.1	0.7 - 1.3	
Platelets (10⁹/L)			0.2
Median	228	238	
IQR	165 - 297	190 - 296	
Creatinine (mg/dL)			0.2
Median	1.03	0.96	
IQR	0.85 - 1.36	0.83 - 1.34	
Alanine aminotransferase (U/L)			0.1
Median	37	45	
IQR	23 - 59	27 - 64	
Lactate dehydrogenase (U/L)			0.04
Median	369	430	
IQR	300 - 479	329 - 532	
Respiratory support			<0.001
O2	242 (88)	36 (58)	
Non-invasive mechanical ventilation	33 (12)	26 (42)	
Cardiovascular disease			0.001
No	175 (64)	52 (84)	
Yes	100 (36)	10 (16)	
History of neoplasia			0.03
No	218 (79)	57 (92)	
Yes	57 (21)	5 (8)	
Diabetes			1
No	219 (80)	50 (81)	
Yes	56 (20)	12 (19)	
Month of admission			0.06
February	9 (3)	0 (0)	
March	223 (81)	46 (74)	
April	39 (14)	16 (26)	
May	4 (2)	0 (0)	

*Data missing for 101 patients.

Data presented as median and interquartile range or frequencies and proportions.

IL: interleukin; IQR: interquartile range.

Supplementary Table 3 - Comparison of baseline descriptive characteristics of patients diagnosed with COVID-19 and hyperinflammatory status who did not receive IL inhibitors vs. patients treated with IL-6 inhibitors.

Variable	No IL inhibitors (n = 275)	IL-6 inhibitors (n = 55)	P value
Age (years)			0.001
Median	68	58	
IQR	58 - 79	52 - 74	
Gender			0.04
Male	201 (73)	48 (87)	
Female	74 (27)	7 (13)	
C-reactive protein (mg/L)			0.5
Median	127	130	
IQR	91 - 169	100 - 195	
*Ferritin (ng/mL)			0.01
Median	1239	1727	
IQR	841 - 1887	1151 - 2757	
Lymphocytes ($10^9/L$)			0.6
Median	0.9	0.8	
IQR	0.6 - 1.1	0.6 - 1.1	
Platelets ($10^9/L$)			1
Median	228	219	
IQR	165 - 297	176 - 299	
Creatinine (mg/dL)			0.3
Median	1.03	1	
IQR	0.85 - 1.36	0.86 - 1.14	
Alanine aminotransferase (U/L)			0.06
Median	37	45	
IQR	23 - 59	30 - 62	
Lactate dehydrogenase (U/L)			0.001
Median	369	458	
IQR	300 - 479	414 - 542	
Respiratory support			<0.001
O ₂	242 (88)	29 (53)	
Non-invasive mechanical ventilation	33 (12)	26 (47)	
Cardiovascular disease			0.01
No	175 (64)	46 (84)	
Yes	100 (36)	9 (16)	
History of cancer			0.03
No	218 (79)	51 (92)	
Yes	57 (21)	4 (8)	
Diabetes			0.04
No	219 (80)	51 (93)	
Yes	56 (20)	4 (7)	
Month of admission			0.02
February	9 (3)	0 (0)	
March	223 (81)	54 (98)	
April	39 (14)	1 (2)	
May	4 (2)	0 (0)	

*Data missing for 107 patients.

Data presented as median and interquartile range or frequencies and proportions.

IL: interleukin; IQR: interquartile range.