Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a recently discovered coronavirus, is responsible for COVID-19, a newly emerged disease that has become pandemic. SARS-CoV-2 infection leads to direct tissue injury, especially of the lungs, but can also trigger an exaggerated host immune response. Indeed, the pathogeny of proinflammatory cytokine storm is now demonstrated in COVID-19.[1] Besides interleukin (IL)-6 blockade,[2] we and others[1] hypothesised that targeting IL-1 should be a safe and effective approach to avoid mechanic ventilation in patients with moderate to severe COVID-19 pneumonia (P-MSP) hospitalised in a non-intensive care unit (ICU). About one-third of P-MSPs experience acute respiratory distress syndrome and/or ICU admission with a lethality rate of 60.5%.[2 3] We observed similar outcomes in our institution and therefore proposed anti-IL-1 blocking by anakinra to nine consecutive P-MSP patients at high risk of worsening who fulfilled the following criteria: age ≥18 years old, SARS-CoV-2 infection confirmed by reverse transcription-PCR on nasopharyngeal swabs, chest CT scan compatible with COVID-19-pneumonia, hospitalised in a non-ICU, oxygen flow of ≤6 L/min, C reactive-protein levels≥50 mg/L. Anakinra was administrated subcutaneously at 100 mg/12 hours from day (D) 1 to D3, then at 100 mg/24 hours from D4 to D10.

Patients' initial characteristics, relevant biomarkers associated with disease severity, including H score,[1] which estimates the risk of having haemophagocytic lymphohistiocytosis (HLH), and outcomes are described in table 1. Among the nine patients, a 47-year-old woman showed an acute respiratory failure 6 hours after the first and only dose of anakinra, leading to premature treatment stop for safety concerns and to ICU admission. No element was subsequently found in favour of anakinra toxicity. The remaining eight analysable patients were non-feverish on the third day and showed good clinical, biological outcomes as

assessed by oxygen flow and blood inflammation markers associated with P-MSP prognosis. C reactive protein (CRP) levels decreased steadily but only partially at D6 days in all, and normalised in 5/8 patients at D11. In all patients, an early chest CT scan controlled between D5 and D8 showed that the extension of lesions had stopped. All nine patients were alive at the last follow-up.

In this small open-label study, anakinra use was safe. Mild transient increase of transaminase and triglyceride levels should not be a major concern and could also reflect subclinical manifestations of secondary HLH due to COVID-19, even though the H scores were moderate in our patients. In bronchoalveolar fluids and lung tissue of patients with COVID-19, highly inflammatory profibrosing monocyte-derived macrophages were shown to be the main inflammatory cells.[4 5] Therefore, IL-1beta/IL-1alpha, the two main paracrine and juxtacrine stimulating cytokines of monocyte-macrophagic cells should figure among the best targets. By acting upstream of the inflammatory signalling pathway induced by inflammasome, anakinra should strongly block the cytokine storm, even if CRP levels in our patients did not decrease as dramatically as can be observed in autoinflammatory diseases. Anakinra, having demonstrated its efficacy in various secondary HLH conditions, it may also be active in COVID-19-related sHLH manifestations. To conclude, this promising, preliminary proof-of-concept study with empirical anakinra doses should encourage and help larger prospective controlled studies to confirm these outcomes and to determine the optimal treatment dosage.

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Table 1 Initial characteristics, including H score,* and outcomes of the nine patients with COVID-19

Patient age/sex/treatment	Risk factors for severe COVID-19	Duration of COVID-19 symptoms (days) before anakinra	Duration of oxygen therapy (days)	D-dimer† (ng/mL) (0–500) D1	Chest CT scan extension (%) at D1	H score*†			Oxygen flow (L/min)			C reactive protein† (mg/L) (0–5)			Triglycerides† (g/L) (0.35–1.7)			Ferritin† (µg/L) (15–300)			Liver Transaminases†		
						D1	D6	D11	D1	D6	D11	D1	D6	D11	D1	D6	D11	D1	D6	D11	D1	D6	D11
P1 55/M/‡	HBP	8	3	242	50	82	63	63	2	0	0	96	18	4	1.2	2.4	3.7	1184	1783	1248	N	3-UN	4-UN
P2 54/M/‡	Obesity	8	5	395	50	96	93	113	3	0	0	177	53	12	1.3	2.4	4.5	1654	837	597	2-UN	2-UN	3-UN
P3 56/M/‡	Obesity	12	3	499	50	68	63	83	3	0	0	282	19	10	1.1	3.3	7	1279	1272	910	N	2-UN	2-UN
P4 55/M/‡	None	7	5	1068	75	112	63	63	3	1	0	248	20	4	1.7	2.5	3.5	1742	854	900	2-UN	6-UN	4-UN
P5 54/M/‡	None	8	2	310	25	33	63	44	1	0	0	83	11	3	1.1	1.6	1.6	961	611	310	N	2-UN	N
P6 84/M/§	HBP Diabetes	8	4	510	25	150	97	62	4	0	0	126	14	1	3	2.1	3	2596	2566	929	N	2-UN	N
P7 62/M/‡	None	4	12	842	25	151	63	44	6	6	2	236	65	16	4	3	1,6	2953	1961	510	N	N	N
P8 60/M/§	HBP, obesity	10	6	456	75	131	79	44	5	0	0	205	26	5	4	3.7	3.5	4563	2613	1338	2-UN	2-UN	N
P9 46/F/‡	Obesity	8	NA	709	25	96	NA	NA	3	NA	NA	86	NA	NA	1.7	NA	NA	388	NA	NA	N	NA	NA
Median (extremes) at D1	NA	8 (4–12)	4.5 (2–12)	477.5 (242–1068)	50 (25–75)	96 (33–151)			3 (1–6)			177 (83-282)			1.7 (1.1–4.0)			1654 (961–4563)			NA		

*H score calculator available online (http://saintantoine.aphp.fr/score/).
†Laboratory analyses on day 1 were performed before starting anakinra.
‡No other specific treatment.
§Hydroxychloroquine and azithromycin.
HBP, high blood pressure; ID, days from anakinra initiation; N, normal range; NA, not applicable; UN, upper limit of normal range.

Letter

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