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Case Report

Use of anakinra in severe COVID-19: A case report

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ABSTRACT

Coronavirus disease 19 is a global healthcare emergency with a high lethality rate. Relevant inflammatory cytokine storm is associated with severity of disease, and IL1 inhibition is a cornerstone treatment for hyperinflammatory diseases. We present here the case of a patient with critical COVID-19 successfully treated with IL-1 receptor antagonist (anakinra).

Introduction

In December 2019, severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) was first discovered in Wuhan, China. Since then, Coronavirus Disease 19 (COVID-19) has risen to a global healthcare emergency, starting in late February 2020 in Northern Italy and rapidly becoming pandemic. The spectrum of symptomatic SARS-CoV-2 infection ranges from mild to critical. While the former accounts for 80% of cases, severe disease with acute respiratory distress syndrome (ARDS) and critical disease with respiratory failure and/or multiple organ dysfunction are diagnosed in 15–30% and 5% of COVID-19 patients, respectively (Wu and McGoogan, 2020). In the first month of the COVID-19 outbreak in Northern Italy, intensive care unit (ICU) admission represented 12% of all COVID-19 patients and 16% of those hospitalized (Grasselli et al., 2020a). Overall, the COVID-19 estimated case fatality rate ranges from 2.3% in China to 7.2% in Italy (Onder et al., 2020). However, in China's virus pandemic epicentre during the early stage of the COVID-19 outbreak, the in-hospital overall lethality rate was higher (28%), and rose up to 62–97% in severely-ill patients requiring mechanical ventilation (Yang et al., 2020). As of March 25, 2020, in Lombardy, Italy, 1591 patients were admitted in ICUs; of them, 405 (26%) had died in ICU, 256 (16%) had been discharged from the ICU, and 920 patients (58%) were still in the ICU (Grasselli et al., 2020).

Early data on changes in clinical and laboratory findings over time demonstrated that levels of d-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase, and interleukin (IL)-6 are higher in non-survivors compared with survivors throughout the clinical course, and their increase paralleled illness deterioration (Guan et al., 2020).

Previous reports demonstrated that a cytokine storm occurs in SARS-CoV-1 and Middle-East Respiratory Syndrome (MERS)-CoV infection, with high levels of IL-1β, IL-6, IL-12, tumor necrosis factor (TNF)α, interferon (INF)-γ and INF-g induced chemokine CXCL10 (Channappanavar and Perlman, 2017). Recent data on COVID-19 support that a relevant inflammatory cytokine storm is associated with severity of disease (Ruan et al., 2020).

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The IL-1 receptor antagonist (anakinra) is a cornerstone treatment for hyperinflammatory conditions such as Still's disease, and has been shown to be highly effective in the treatment of *cytokine storm syndromes*, including macrophage activation syndrome and cytokine release syndrome (La Rosèe et al., 2019). Anakinra has a very safe profile and high dosages have been used even in patients with severe viral infection (EBV, H1N1 and Ebola) (van der Ver et al., 2015).

We present here the case of a patient with critical COVID-19 successfully treated with anakinra.

Case report

On February 28, 2020 an otherwise healthy 50 year-old man was admitted to the local Hospital in Crema, Lombardy because of fever and dyspnea. Infection with SARS-CoV-2 was confirmed by RT-PCR on nasopharyngeal swab and chest computerized tomography scan showed bilateral ground glass opacities. The patient was put on non-invasive ventilation and antiviral therapy with lopinavir/ritonavir, and hydroxychloroquine was started. At day 3, his condition worsened requiring ICU admission at our Hospital for invasive mechanical ventilation and hemodynamic support. On ICU admission, the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) was 160 on pressure control ventilation, with positive end expiratory pressure (PEEP) 12 and FiO2 50%. High levels of acute phase reactants and progressive liver cholestatic injury were observed (Table 1). Hepatic involvement with liver enzymes higher than five-fold their upper limits contraindicated treatment with remdesivir or tocilizumab. At day 10, considering the patient's critical condition (PaO2/FiO2 85, volume control ventilation PEEP 14 FiO2 50%) and the hyperferritinemic inflammatory status with ferritin levels more than 3000 ng/ml, use of off-label anakinra was considered and started with the following dosage schedule: 200 mg intravenously followed by 100 mg every 6 h subcutaneously. Lopinavir/ritonavir and hydroxychloroquine were interrupted and no other immunosuppressive or immunomodulatory drug, including glucocorticoids or immunoglobulins, was started. In the next 72 h, a sharp reduction of inflammatory markers and ferritin, an increase in lymphocyte count and a significant reduction of liver enzymes were observed (Table 1). Respiratory parameters improved by day 13 (PaO2/FiO2 270, pressure control ventilation PEEP 10 FiO2 30%), followed by a favourable radiographic evolution. At day 18 the patient was discharged from the ICU.

In the following days, respiratory function progressively improved. On day 21, 4 days after ICU discharge, the patient became febrile with increase in C-reactive protein levels and no alteration in ferritin levels. Considering the persistent improvement in respiratory function and on suspicion of central venous catheter-related bacteremia, anakinra was stopped. The intravenous catheter was removed and empiric antibiotic treatment was started with vancomycin plus piperacillin/tazobactam, modified 2 days later to cefazolin according to the identification of methicillin-sensitive *Staphylococcus aureus* in blood culture. A complete and prompt response to antibiotic treatment was observed with normalization of acute phase reactants. The patient was discharged from the hospital at day 29 in healthy condition and normal oxygen saturation on room air.

Discussion

To our knowledge, this is the first report of a critical case of COVID-19 effectively treated with anakinra.

Current management of COVID-19 is supportive, as respiratory failure from ARDS is the leading cause of mortality. Vaccines and approved targeted therapies for SARS-CoV-2 infection are still lacking and a multitude of compounds are now under investigation. The need to urgently identify an effective approach to manage COVID-19 led to the testing of existing antiviral drugs commonly used for other viral infections (i.e., interferon, ribavirin, and lopinavir-ritonavir), at present with controversial results (Cao et al., 2020). Remdesivir is a promising novel nucleotide analogue with in vitro activity against SARS-CoV-2 and proven activity against SARS-CoV-1 and MERS-CoV both in vitro and in animal studies (Sheahan et al., 2020).

Recently a cytokine storm resembling secondary haemophagocytic lymphohistiocytosis (sHLH) has been suggested to drive a later hyperinflammatory stage of COVID-19, with a decisive role in poor prognosis (Huang et al., 2020). sHLH is a hyperinflammatory syndrome characterised by life-threatening hypercytokinaemia leading to multiorgan failure. A cytokine profile resembling sHLH, characterized by increased levels of IL-2, IL-7, granulocyte-colony stimulating factor, INF-γ, CXCL10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and TNFα was described in severe COVID-19 (Huang et al., 2020). Predictors of mortality from a retrospective, multicentre study of 190 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1435.3 mcg/L in non-survivors *vs* 503.2 mcg/L in survivors) and IL-6 levels (Grasselli et al., 2020), suggesting that higher mortality rates may be associated with a virally driven hyperinflammation.

Table 1
Course of laboratory tests and respiratory parameters over time

	Day 0 Hospital admission	Day 3 ICU admission	Day 9	Day 10 Anakinra administration	Day 11	Day 13	Day 18 Discharge from ICU	Day 21 Stop anakinra	Day 29 Discharge from hospital
WBC count, $\times 10^9$/l	4.9	6.9	5.8	9.7	10.8	10.9	10.6	9.07	6.14
Lymphocyte count, $\times 10^9$/l	0.6	0.3	0.5	1.0	0.6	0.9	1.0	1.17	1.67
Hemoglobin, g/dl	11.5	9.9	9.8	10.4	9.9	9.1	9.1	9	10.6
PLT count $\times 10^9$/l	191	215	362	444	429	473	507	513	330
Ferritin, ng/ml				3042	1936	1040	648	738	497
CRP, mg/dl	10.5	20.4	8.8	8.6	11.3	3.2	2.4	4,4	0.3
AST, U/l			188	182	94	43	29	29	
ALT, U/l	18	20	224	384	307	188	90	73	11
GGT, U/l	48	107	276	586	562	442	344	299	110
Bilirubin, mg/dl			2.1	2.0	0.9	0.6	0.8	0.92	0.66
LDH, U/l	300	289	334	334	267	219	233	278	180
Creatinine, mg/dl	0.8	0.9	0.8	0.7	0.5	0.6	0.6	0.6	0.65
Fibrinogen, mg/dl	472	707	881		929	618	506	426	
D-dimer, ug/l	423	429	837		1834	1352	4684	4082	1025
PaO2/FiO2	160	182	109	85	85	270	310		Oxygen saturation 97% on room air

WBC: white blood cell; PLT: platelet count; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase; LDH: lactic dehydrogenase; PaO2: arterial oxygen partial pressure; FiO2: fraction of inspired oxygen.

The possible role of anti-cytokine treatment with IL-6 inhibitor (tocilizumab) in respiratory failure associated with COVID-19 has been recently proposed (Xu et al., 2020). In inflammatory cytokine storms, IL-1 is a key effector and its role in promoting pro-inflammatory cytokines, including IL-6, is well known (Dinarello et al., 2012). Indeed, IL-1 inhibitor anakinra has been shown to be highly effective in the treatment of cytokine storm syndromes (Dinarello et al., 2012) and has already been proven safe in patients with sHLH associated with viral infections such as EBV, H1N1 and Ebola (van der Ver et al., 2015). Its short half-life makes it a drug to be used widely in clinical practice and also in critically ill patients to overcome situations in which a prompt treatment interruption is required, such as bacteraemia as described above.

This first report suggests that in the cytokine storm occurring during severe COVID-19, IL1 inhibition may represent a safe and promising strategy to reduce inflammation preventing multi-organ dysfunction, and an appropriate tailored treatment strategy is crucial.

Further larger cohort observations are needed to confirm the possible association with positive clinical outcomes. To date, May 5, 2020, 12 clinical trials on anakinra in COVID-19 patients are registered on ClinicalTrials.gov, 7 of them recruiting patients. These on-going studies will provide key information on safety and efficacy of anakinra in the hyperinflammatory response to SARS-CoV-2.

Conflict of interest

Authors declare no conflict of interests.

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