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Sars-Cov-2 Virus, Cytokine Storm and Tocilizumab- A Case Report

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Abstract

On March 11, 2020, the World Health Organization (WHO) announced the SARS-COV-2 (severe acute respiratory syndrome coronavirus 2) infection, known as COVID-19 (coronavirus disease 2019) as a pandemic.

There is no specific antiviral treatment for Covid-19 and several drugs have been proposed as a potential treatment, but it seems that one of the most promising avenues against SARS-COV-2 is to administer immunomodulatory drugs that reduce the cytokine storm.

We report here the case of a patient with respiratory failure linked to COVID-19 who had a favorably rapid after infusion of the anti-interleukin 6 receptor inhibitor: Tocilizumab.

Keywords: *COVID-19, SARS-COV-2, Cytokine storm, Anti-interleukin 6 receptor inhibitor, Tocilizumab, Intensive care.*

Introduction

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection, called COVID-19 (coronavirus disease 2019) started in December 2019 in the Wuhan region of China. It is the cause of life-threatening pneumonia and has spread globally to the point of becoming a pandemic.

The pathogenesis of coronavirus disease 2019 (Covid-19) involves a cytokine storm with elevated serum levels of pro-inflammatory cytokines and chemokines: IL6, Tumor necrosis factor (TNF-alpha), Interferon-gamma, IL1, IL12, IL8, IL2, IL7, IL10, Gamma interferon-induced protein (IP10), Chemo-attractive protein (MCP1), Inflammatory macrophage protein (MIP1A) [7].

One of the most promising avenues against SARS-CoV-2 is to administer immunomodulatory drugs that would curb the heat of the immune system. Several are being tested, and Tocilizumab has just shown encouraging results [6].

Medical Observation

This is a 52-year-old patient with a history of type 2 diabetes on oral antidiabetics drugs, declared COVID-19 following screening with an initially normal chest CT scan.

On admission, the patient was eupneic with 98% open-air oxygen saturation with PAO2/FIO2=206, normocardium at 96 bpm/min, normotensive at 12/8 and afebrile.

Laboratory assessment: Hyperleukocytosis at 11880, Lymphopenia at 370, Ferritinemia at 993 ng/ml, CRP at 7 mg/l, PCT at 0.16, Troponin at 1.2 µg/l, BNP at 58 pg/ml, D-Dimer at 240 µg/l.

Treatment was started with Azithromycin, Hyroxychloroquine, 3rd generation cephalosporin and quinolone. On D2 of hospitalization, the patient had presented with 88% desaturation, polypnea at 35 cycles/min with PAO2/FIO2=73. Biologically: lymphopenia at 310, ferritinemia at 3814 ng/ml, CRP at 139 mg/l, D-Dimer at 710 µg/l.

A thoracic CT angiography was done which showed the presence of parenchymal involvement related to the COVID-19 infection with no signs in favor of pulmonary embolism. (Figure 1).

ICONOGRAPHY:

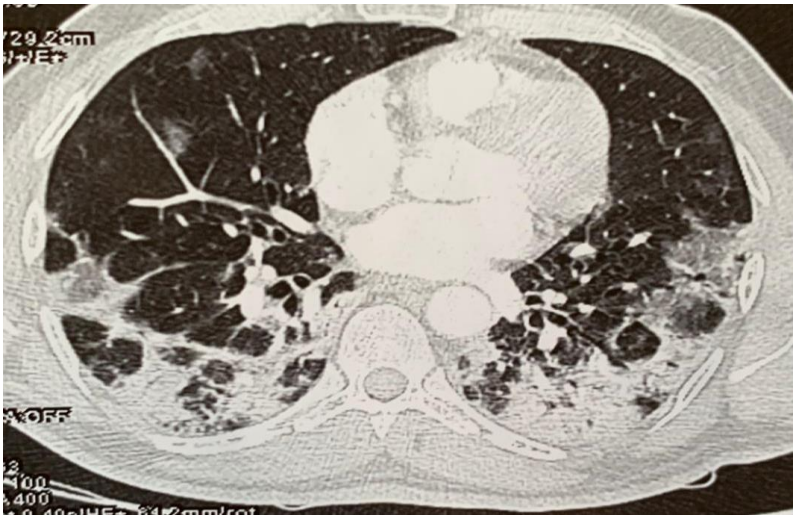


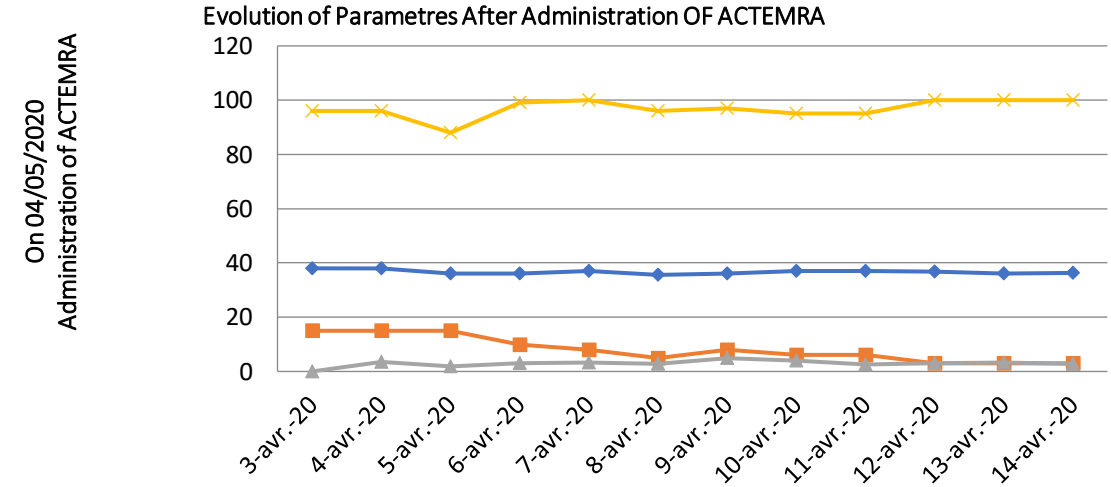
Figure 1: Thoracic tomography.

Faced with this clinical, biological and radiological worsening, an interleukin 6 dosage was taken: 21.6 pg/ml (normal value at 7 pg/ml).

The decision was to:

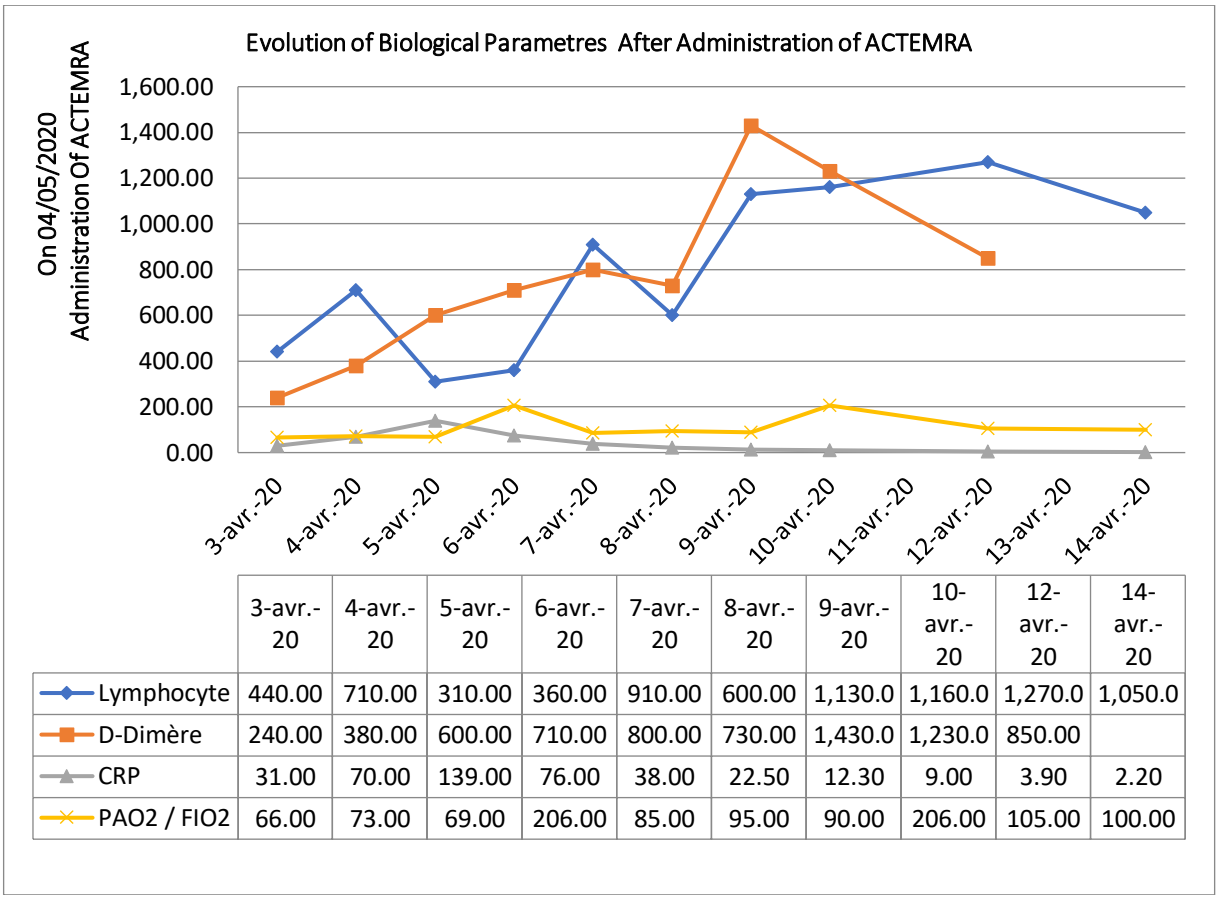
- Administration of Tocilizumab (Actemra) 400 mg.
- Alternating sessions of NIV and high concentration mask.
- Continuation of initial treatment.

The evolution was marked by marked clinical as well as biological improvement. (Figure 2 and 3). The patient is declared out on D14 of his hospitalization after negativation of the COVID PCR.



	3-avr.-20	4-avr.-20	5-avr.-20	6-avr.-20	7-avr.-20	8-avr.-20	9-avr.-20	10-avr.-20	11-avr.-20	12-avr.-20	13-avr.-20	14-avr.-20
Température	38	38	36	36	37	35.6	36	37	37	36.7	36.1	36.3
Besoin en oxygène	15	15	15	10	8	5	8	6	6	3	3	3
Diurèse	0	3.5	1.8	3.1	3.2	2.8	4.9	3.9	2.5	3	3.2	2.7
saturation	96	96	88	99	100	96	97	95	95	100	100	100

Figure 2: Evolution of parameters after administration of Actemra.



	3-avr.-20	4-avr.-20	5-avr.-20	6-avr.-20	7-avr.-20	8-avr.-20	9-avr.-20	10-avr.-20	12-avr.-20	14-avr.-20
Lymphocyte	440.00	710.00	310.00	360.00	910.00	600.00	1,130.0	1,160.0	1,270.0	1,050.0
D-Dimère	240.00	380.00	600.00	710.00	800.00	730.00	1,430.0	1,230.0	850.00	
CRP	31.00	70.00	139.00	76.00	38.00	22.50	12.30	9.00	3.90	2.20
PAO2 / FIO2	66.00	73.00	69.00	206.00	85.00	95.00	90.00	206.00	105.00	100.00

Figure 3: Evolution of biological parameters after administration of Actemra.

Discussion

The pathogenic mechanism of the immune response against the Sars-Cov-2 virus in the pulmonary alveoli is as follows: [6]

- The virus infects alveolar epithelial cells; mainly type 2 pneumocytes in lung tissue, thanks to its anchoring on a receptor.
- The destruction of lung cells where the corona viruses have proliferated by replication of their RNA, and the increase in their cell permeability, results in the release of viruses.
- There is an awakening of the innate immune system by which the players in the host's defense (macrophages, lymphocytes, monocytes, and granulocytes) not only start capturing the virus but also produce a discharge of chemokines and cytokines including IL-6.

IL-6 has two forms of receptors: one attached to the membrane of cells, the other soluble. The binding of IL-6 to its soluble receptor results in the formation of a complex, which can in turn bind to the membrane glycoprotein gp130, inducing the transduction of an intracellular signal, itself responsible for triggering the pro-inflammation [7].

Tocilizumab is a monoclonal antibody usually prescribed in rheumatology. Its action consists of blocking the membrane and soluble receptors of interleukin IL6, constituting a potential therapeutic option in severe forms of Covid-19.

Efficacy data on clinical outcomes come from two non-comparative observational studies of insufficient evidence. Their results indicate that tocilizumab appears to provide benefits in terms of reducing inflammatory markers and improving the clinical condition of patients in severe or critical condition. While encouraging and confirming the biological plausibility of a possible efficacy in the context of cytokine release syndrome linked to Covid-19.

The French study by a team from Foch Hospital, Suresnes. In collaboration with Paris-Descartes University in Paris, she tested tocilizumab on thirty patients, aged under 80, with a severe form which worsened rapidly. After an average of eight days, the condition of the patients treated, compared to that of the control group, improved significantly to the point of providing most respiratory assistance. In addition, very few side effects were noted, and the drug appears to be well tolerated [6].

The Chinese study involved 20 patients with severe disease. A day after they were given tocilizumab, the fever went down. After five days, most were less dependent on respiratory assistance, and one patient was completely dispensed with. Another notable improvement is that abnormally high levels of C-reactive protein in the blood were significantly reduced in over 80% of patients. All the patients recovered after 10 to 31 days of treatment, and again, there were no side effects [2,3,9].

However, a number of jurisdictions recommend the use of different molecules alone or in combination. The Italian,

Spanish, Chinese guidelines recommend the use of tocilizumab in critically ill patients who suffer from cytokine release syndrome and to consider using this molecule on an individual basis in patients with inflammation persistent (elevated IL-6, CRP, D-dimer and ferritin) and ARDS requiring mechanical ventilation without evidence of bacterial superinfection or sepsis. A dose equivalent to 4 to 8 mg per kg of body weight diluted in saline solution and administered by intravenous infusion over more than one hour is recommended. The usual dose therefore varies from 400 mg to 600 mg and should not exceed 800 mg. In patients whose clinical condition has not improved, a second dose may be given 12 hours after the first. The Spanish guide mentions that a third dose could be considered in the event of worsening of the clinical parameters associated with a persistence of fever. For other jurisdictions, treatment should be limited, in general, to supportive care [4,5,6,8,9].

Twenty-seven clinical studies are currently underway both in Canada and internationally; they assess the efficacy of tocilizumab, sarilumab or siltuximab in hospitalized patients whose majority of clinical practice guidelines state that there is not currently sufficient evidence to recommend a specific treatment for subjects with Covid -19 is severe or critical [1].

This observation enabled the medical staff to make the decision to introduce tocilizumab as adjunct therapy in the face of a cytokine storm.

Conclusion

The current recommendations are still in the preliminary stages to be able to draw definitive conclusions because the disease is very recent and growing. In the wake of the pandemic, double-blind, placebo-controlled randomized clinical trials are therefore still necessary to establish, on the one hand, whether tocilizumab is really effective in patients infected with Covid-19 in a situation of acute respiratory failure, and, on the other hand, the clinical stage of the disease at which the product should be used. The safety profile of tocilizumab and its possible drug interactions will also have to be established in clinical trials.

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