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Short Communication

Facing the SARS-CoV-2 (COVID-19) outbreak with IL-6R antagonists

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As of April 10th, 2020, the outbreak of SARS-CoV-2/COVID-19 infection has affected 1,673,423 people worldwide, with 157,053 confirmed cases in Spain of and a total of 15,447 deaths according to John Hopkins Coronavirus Resource Center.* These numbers are tremendously discouraging, and time will come to review what could have been done much better and sooner. Barcelona, as a big city in Southern Europe, had 19,4 million tourists, with 21,324 million of revenues in 2019. Since March 14th, the city is fully desertic. During the outbreak the one good thing to highlight has been the excellent coordination among rheumatologists, internal medicine specialists, infectious disease physicians, and global health care workers fighting round the clock the pandemic.

Facing the outbreak in Europe, we realized that data from China did not help to understand the overwhelming situation. A unique recent retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China, described a pattern of acute infection and severe hyperinflammation with an elevated ferritin over 1297·6 ng/mL in non-survivors and IL-6 levels as the only available information to understand the clinical picture of the disease (1). More recently, several papers have put some light on the clinical course and risk factors for mortality of adult inpatients as well as the definition of clusters with severe respiratory illness similar to a severe acute respiratory syndrome (SARS) coronavirus associated with ICU admission and high mortality (2-4).

To date, we recognize the weakness of the recommendations for the treatment of SARS-CoV-2 infection. The context of emergency and the absence of randomized controlled trials (RCT) lacks evidence of any proposal to face the massive demand for agreement among countries. Therefore, several points must be raised. Firstly, the importance of testing all the populations such as South Korea (10,450 confirmed cases) did, rather than favoring a strategy of mitigation, allowing COVID-19 to spread slowly without overwhelming the health system declared in Sweden (9,685 confirmed cases). On the other hand, the need for prophylaxis and launching strong recommendations for all health care workers in the front line.

Treatment with hypothetic options

The concern for treatment has brought paradoxical measures such as the debate for the use of corticosteroids, antiretrovirals, OH-chloroquine plus azithromycin regimens, which are the biological therapies to assay or the management of non-invasive ventilation in the absence of RCT. The current focus has been on the development of novel therapeutics, including antivirals and vaccines, but we will have to wait a bit to have robust proposals. Corticosteroids have been not recommended by World Health Organization (WHO) according to recent reviews analyzing the data from previous pandemics by SARS and the Middle East respiratory syndrome (MERS), because they might exacerbate COVID-19-associated lung injury (5, 6). There are no reliable studies that have evaluated the efficacy and safety of corticosteroids in patients with COVID-19. Available data from studies in patients affected by other viral infections are conflicting and, in some cases, subject to multiple biases, although many highlights that those may produce various unwanted effects in patients. Despite these, some scientific societies have defined situations in which to use corticosteroid treatment to alleviate the uncontrolled inflammatory response caused by the virus, although there is not unanimity in their recommendations (7).

Biological therapies (bDMARD´s) and targeted synthetic (ts) DMARDs (the Janus kinase (JAK) inhibitors tofacitinib, baricitinib) are under the light nowadays. Guidelines from different hospitals and societies suggest different strategies for them to be used (8, 9). Single-center experiences may provide in the next few months valuable information about this issue.

Either way, accumulating evidence suggests that a subset of patients with severe SARS-CoV-2 might have a severe immune activation ("cytokine release syndrome" CRS) in response, causing acute respiratory dis-

* Since the moment we started soon this morning writing this editorial, the total number of people infected worldwide is 1,631,310, this means 29,094 more. In Spain, the number of deaths increased by 396 people.

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tress syndrome (ARDS), a sepsis-like picture leading to a multi-organ damage. This is certainly caused by a release of different cytokines such as IL-2, IL-7, IL-10, interferon-γ, macrophage inflammatory protein 1-α, and tumor necrosis factor-α, but above all, IL-6. IL-6 is a cytokine with pleiotropic activity. When produced mainly by macrophages, dendritic cells and fibroblasts in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), performs a protective function against the virus healing damaged tissue through induction of acute phase and immune responses. The cytokine storm is reminiscent of secondary hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) which can be triggered by a viral infection (10, 11).

Nevertheless, it is essential to acknowledge that severe cases of COVID-19 infection with active cytokine release are not a CRS yet until pathology confirmation. IL-6 contributes to host defense against the infection; however, exaggerated synthesis of IL-6 while fighting environmental stress leads to an acute severe systemic inflammatory response. Therefore, high levels of IL-6 can activate the coagulation pathway and vascular endothelial cells but inhibit myocardial function. In the subset of patients with severe SARS CoV-2 infection this cytokine engine activation presents with recognized features such as high plasma levels of C-reactive protein (CRP), D-dimer, alanine transaminase (ALT) and aspartate transaminase (AST), ferritin, decrease of lymphocyte count, and elevation of lactate dehydrogenase (LDH) (3).

Treatment with IL-6R antagonists

On August 30, 2017, the U.S. Food and Drug Administration approved Actemra (tocilizumab, Genentech, Inc., South San Francisco, CA) for the treatment of severe or life-threatening chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS) in adults and in pediatric patients (12). This approval eased the use in the present pandemic situation. Tocilizumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that blocks IL-6 from binding to the soluble and membrane-bound IL-6R, many years ago developed as an intravenous (IV) infusion, but years later also subcutaneously (13). The efficacy and safety of tocilizumab IV were previously demonstrated either as monotherapy, in adult patients or in combination with disease-modifying antirheumatic drugs (DMARD) in adult patients with RA. Tocilizumab is currently approved as an IV formulation to treat rheumatoid arthritis (RA) and giant cell arteritis (GCA), in the USA and Europe (14).

Given our experience treating RA and GCA, and TCZ usefulness in CRS complicated by T-cell engaged therapy, we hypothesize the potential beneficial effects of IL-6 blockade receptor in SARS-CoV-2 coronavirus patients with an acute onset of CRS (15).

We did a set of health recommendations and an algorithm to be followed to treat the SARS-CoV-2 infection, based on weak data published. Our initial guidelines included as a first step the treatment with OH-chloroquine 400mg/12h (1d) followed by 200mg/12h (4 more days) plus azithromycin 500mg/d (3 days). Patients with radiological progression (Figure 1), increased oxygen needs, and progressive increase of CRP, D-dimer, and ferritin were considered candidates to initiate TCZ treatment. According to more than one of the following criteria: 1) Age-adjusted Charlson Comorbidity Index scores<4, 2) Interstitial pneumonia with severe respiratory failure (score=2), 3) rapid respiratory worsening requiring non-invasive or invasive ventilation (score≥3 on the COVID respiratory severity scale), we then confirmed the presence of severe systemic inflammatory response criteria (adults): high levels of IL-6 (>40 pg/mL) (alternatively high levels of D-dimer (>1500 ng/mL) or progressively increasing D-dimer. If so, patients were treated with Tocilizumab (if ≥75 kg: a single dose of 600 mg), less than <75 kg: a single dose of 400 mg. Exclusion criteria for IL-6R antagonist therapy were: AST/ALT values greater than 5 times the upper limit of normality, Neutrophils <500 cells/mmc, Platelets <50000 cells/mmc, sepsis documented by other pathogens other than SARS-CoV-2,

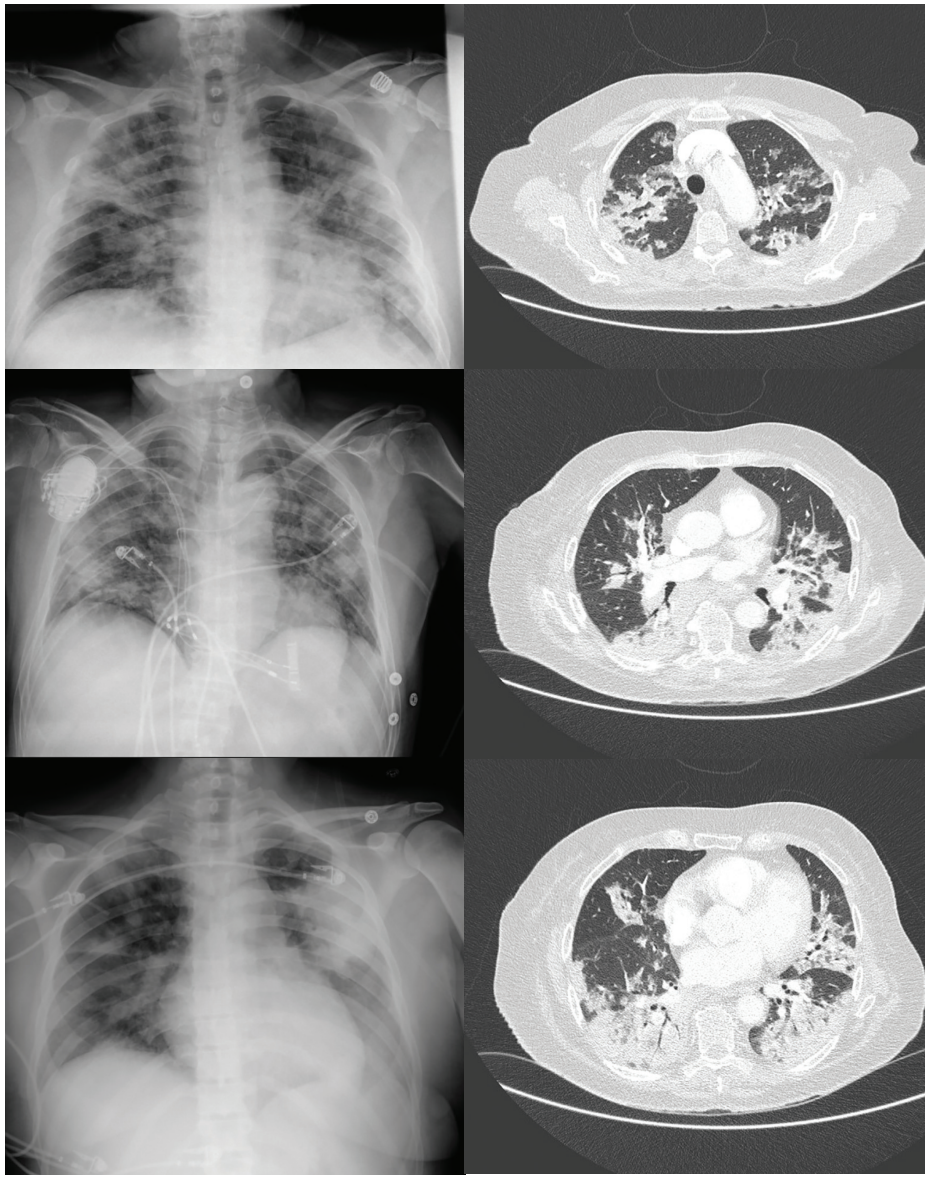

Figure 1. Chest X-Ray showing extended bilateral consolidation. Transverse CT scan from patients with severe Covid-19 infection showing multiples lobular and subsegmental areas of consolidation combined with few ground-glass opacities diffusely distributed.

presence of comorbidity that can lead, according to clinical judgment, to a poor prognosis, complicated diverticulitis or intestinal perforation, or ongoing skin infection (uncontrolled pyodermitis with antibiotic treatment). To date, more than 100 patients (range 27-75yo) have received Tocilizumab with a satisfactory response after blocking IL-6R (data not published). Few patients who initially did not respond to a single dose, received a second one. Now, in April 2020, we treat patients with a single dose according to Spanish National Agency (AEMPs) recommendations. We alternatively treated five patients with sarilumab 200mg/sc, also with a successful response because of patient profile or lack of tocilizumab.

The treatment of cytokine storm is somehow unknown. The rapid and simultaneous combination of supportive care and RCTs is the only way to find effective treatments with safety profile for COVID-19 (16). Meanwhile, IL6 R blockers (tocilizumab, sarilumab and siltuximab) may have a role for treating moderate to severe patients. However, not only when the disease is entirely ripped over. With our recent experience treatment also may be successful in early stages of cytokine release syndrome (CRS). If they can effectively block the signal transduction pathway of IL-6, thus tocilizumab, sarilumab and siltuximab are likely to emerge as effective drugs for patients with moderate to severe COVID-19.

In the nearest future, hundreds of randomized clinical trials and data from case-control studies will ease the management of the tail of the present pandemic and prepare for any other future outbreak. Physician-derived data from the rheumatology COVID-19 registry will enable rheumatologists to accumulate a rapid, worldwide case series with which to compare trends in COVID-19 outcomes across diseases, therapies and countries (17).

The good news, for now, is that to date in Spain, 53,165 have recovered from the worst health and economic impact since the civil war.

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