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Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review

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ABSTRACT

Severe Acute Respiratory Syndrome related to Coronavirus-2 (SARS-CoV-2), coronavirus disease-2019 (COVID-19) may cause severe illness in 20% of patients. This may be in part due to an uncontrolled immune-response to SARS-CoV-2 infection triggering a systemic hyperinflammatory response, the so-called “cytokine storm”. The reduction of this inflammatory immune-response could be considered as a potential therapeutic target against severe COVID-19. The relationship between inflammation and clot activation must also be considered. Furthermore, we must keep in mind that currently, no specific antiviral treatment is available for SARS-CoV-2. While moderate-severe forms need in-hospital surveillance plus antivirals and/or hydroxychloroquine; in severe and life-threatening subsets a high intensity anti-inflammatory and immunomodulatory therapy could be a therapeutic option. However, right data on the effectiveness of different immunomodulating drugs are scarce. Herein, we discuss the pathogenesis and the possible role played by drugs such as: antimalarials, anti-IL6, anti-IL-1, calcineurin and JAK inhibitors, corticosteroids, immunoglobulins, heparins, angiotensin-converting enzyme agonists and statins in severe COVID-19.

Abbreviations: ACE-2, Angiotensin-converting enzyme-2; AD, Autoimmune diseases; ADE, Antibody dependent enhancement; ADRS, Acute distress respiratory syndrome; APC, Antigen-presenting cells; aPL, Antiphospholipid antibodies; CD, Cluster of differentiation or cluster of designation or classification determinant; CDC, Centres for disease control; COVID-19, Coronavirus disease 2019; CQ, Chloroquine; CyA, Cyclosporine A; FDA, Food and Drugs Administration; GCS, Glucocorticoids; HCQ, Hydroxychloroquine; HPS, Haemophagocytic syndrome; IFN-γ, Interferon gamma; IL, Interleukin; JAK, Janus-Kinase family of enzymes (JAK1, JAK2, JAK3, TYK2); IVIG, Intravenous immunoglobulins; MDAS, Melanoma differentiation-associated gene 5; MHC-II, Major histocompatibility type-II; LMWH, Low-molecular weight heparin; MAS, Macrophage activation syndrome; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; mTOR, Mammalian target of Rapamycin; NHC, National Health Council; NK, natural killer cells; NF-κβ, Nuclear Factor-κβ; PIC, Pulmonary intravascular coagulation; PTE, Pulmonary thromboembolism; RA, Rheumatoid arthritis; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; SLE, Systemic Lupus Erythematosus; TCZ, Tocilizumab; TLR, Toll-Like Receptor; TNF-α, Tumour necrosis factor-alpha; TRAAVIR, Thrombotic Risk Associated with Antiphospholipid Syndrome after Viral infection; TRALI, Transfusion-related acute lung injury; TGF-β, Transforming growth factor-beta; Tregs, Regulatory T-cells; WHO, World Health Organization

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Variables related to high risk to develop severe COVID

1. Older age (> 65 years old)
2. High Sequential Organ Failure Assessment [SOFA] score
3. Comorbidities:
   - Hypertension
   - Cardiovascular (mainly, coronary heart disease)
   - Diabetes Mellitus
4. Laboratory test
   - D-dimer levels > 1 μg/mL on admission

* The role played by obesity, smoking, asthma, hyperferritinemia and high IL-6 levels as risk factors for severe COVID are not clearly established to date.
with sera of patients that contains non-neutralising antibodies could enhance disease by promoting virus infection in monocytes/macrophages or by inducing complement activation leading to vascular injury such as systemic necrotising vasculitis and disseminated intravascular coagulation. Furthermore, ADE up-modulates the immune response and can elicit sustained inflammation, lymphopenia, and cytokine storm, as documented in COVID-19 severe cases [26]. It could happen in relapsing COVID-19 patients possessing naturally acquired or passively administered antibodies against SARS-CoV-2, or in patients previously exposed to other coronaviruses. A mechanism for ADE in SARS-CoV-2 could be the evasion of neutralising antibodies against Spike protein produced in previous virus infection [27]. ADE in SARS-CoV-2 may account for the geographic discrepancy in the pathogenesis. Thus, an individualised monitoring of the harshest cases in order to identify coagulopathies associated with hyperinflammatory syndrome and, consequently, to treat them with immunosuppressing drugs could be a good approach.

The advent of biologic therapies that target cytokines has expanded the armamentarium of treatments available for HPS/MAS and for severe infections. Notably, individualised monitoring of the harshest cases in order to identify coagulopathies associated with hyperinflammatory syndrome and, consequently, to treat them with immunosuppressing drugs could be a good approach.

The advent of biologic therapies that target cytokines has expanded the armamentarium of treatments available for HPS/MAS and for severe infections. Notably, individualised monitoring of the harshest cases in order to identify coagulopathies associated with hyperinflammatory syndrome and, consequently, to treat them with immunosuppressing drugs could be a good approach.

3. Review of the literature

3.1. Search strategy and selection criteria

Data for this review were obtained through a comprehensive literature search using the keywords: “immunosuppressives”, “anti-malarials”, “hydroxychloroquine” “chloroquine”, “anakinra”, “tocilizumab”, “corticosteroids”, “heparin” “low-molecular-weight heparin” “immunoglobulins”, “sarilumab”, “JAK inhibitors”, “cyclosporine” “ACE inhibitors” “statins” “haemophagocytic syndrome” “acute respiratory distress syndrome”. The search was restricted to: “SARS-CoV-2”, “COVID-19”, “treatment”, to identify articles published in English from MEDLINE, PubMed and The Cochrane Library (January 2020–March 30th, 2016). Some interesting papers related to SARS-CoV, MERS, thrombosis-related viruses, cytokines and inflammation from 2003 were also reviewed and included according to their relevance. Clinical trials, case-control or cohort studies, brief reports, communications, reviews and systematic reviews were included. Current national guidelines on management of COVID-19 were also reviewed and included (CDC, Australian, WHO, Spanish and Italian). The authors reviewed the selected manuscripts and finally the most appropriated were included for this review.

4. Results and discussion

4.1. Antimalarials

Old anti-infectious drugs, such as chloroquine (CQ) and hydroxychloroquine (HCQ) firstly used as anti-malarial drugs and later as immunomodulatory treatment for autoimmune and rheumatic diseases, mainly SLE and rheumatoid arthritis, have also shown a potential antiviral effect against SARS and avian influenza H5N1. Their effects are related to the change of cell membrane pH necessary for viral fusion and the interference with glycosylation of viral proteins. Furthermore, CQ/HCQ appear to have a summatory anti SARS-CoV-2 effects when administered with antivirals [29] and with azithromycin [30] We would stress on other possible pleiotropic effects of CQ/HCQ other than anti-infectious. Antimalarials have many anti-inflammatory, anti-aggregant and immune-regulatory properties: they inhibit phospholipase activity, stabilize lysosomal membranes, block the production of several pro-inflammatory cytokines and, in addition, impair complement-dependent antigen-antibody reactions [31,32]. Currently, at least twenty clinical trials have already been registered to test the usefulness of CQ and HCQ for the treatment of COVID-19 [33]. The just finished Chinese clinical trial - ChiCTR2000029559 – have shown the potential of HCQ in the treatment of COVID-19 (Chen Z, et al.: submitted). In vivo results, although promising, are limited to date. Thus, considering the antiviral and immunomodulatory properties of the anti-malarials and the pre-clinical evidence of effectiveness and safety from long-time clinical use for other indications, clinical research on CQ/HCQ in patients with COVID-19 is warranted [34]. So, on the basis of the weak evidence available, treatment guidelines have already incorporated the use of CQ/HCQ for treating patients with COVID-19. Thus, HCQ associated with other drugs could play a role in the treatment of SARS-CoV-19 infection [35].

4.2. Interleukin-6 blockade (anti-IL-6)

Tocilizumab (TCZ), is an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R. The main indication of the TCZ use is rheumatoid arthritis [36] and giant-cell arteritis [37]. In 2017, the U.S. Food and Drug Administration (FDA) approved TCZ for the treatment of cytokine release syndrome (CRS) consisting of a systemic inflammatory response caused by the massive release of pro-inflammatory cytokines in response to iatrogenic (e.g. CAR-T therapies) or infective stimuli [38].

In COVID-19 patients, IL-6 plasmatic levels were especially high in severe cases. Histological examination of lung tissue showed diffuse alveolar damage with cellular fibrinoid exudates and interstitial mononuclear inflammatory infiltrates suggesting severe immune injury in a biopsy sample from a severe COVID-19 patient [39]. A case series in 20 Chinese patients reported that TCZ allowed the lung lesion opacity to be erased in 19 patients (90.5%), oxygen intake lowered in 15 (75%) and oxygen stopped in one case. Moreover, elevated C-reactive protein decreased significantly in 84.2% of the patients, lymphocytes count normalised in 52.6% patients [40]. In China TCZ was recently approved for patients affected by severe SARS-CoV-2 pulmonary complications by the National Health Commission of the People's Republic of China. Further, a randomised controlled clinical trial is ongoing in China (ChiCTR2000029765) [41]. In this way, sarilumab [Sanofi / Regeneron] is an anti-human IL-6 receptor monoclonal antibody launched for the treatment of rheumatoid arthritis. Sarilumab is able to block the IL-6 as the form that TCZ does and could exert positive effects in cases of COVID-19 with severe manifestations and high IL6 levels. Currently, a phase II-III clinical trial has started in United States of America and five European countries [42].
4.3. Interleukin-1 blockade (anti-IL-1)

Anakinra, an anti-IL-1, is another therapeutic option for treating patients suffering of severe COVID-19. It is a recombinant and slightly modified version of the human interleukin 1 receptor antagonist protein (IL-1Ra). It is naturally secreted by monocytes and tissue macrophages that selectively binds to IL-R and modulates its activity. The blockade of IL-1 leads to the inhibition of inflammatory responses [43]. In a phase 3 randomised controlled trial the IL-1 blockade (anakinra) in sepsis has been shown as beneficial with increased survival without increased adverse events [44]. Thus, considering the similar “cytokine storm” between severe sepsis and severe COVID-19, anakinra may play a role in the treatment of some severe or refractory cases.

4.4. Interleukin-2 inhibition

The cyclosporine-cyclophilin A complex inhibits a calcium/calmodulin-dependent phosphatase, calcineurin, the inhibition of which is thought to suppress organ rejection by halting the production of the pro-inflammatory molecules TNF-α and interleukin 2 (IL-2). Due to these effects, cyclosporine A (CyA) has been proven very useful in the management of autoimmune diseases. Cyclophilin is also known to be recruited by the Gag polyprotein during HIV-1 virus infection, and its incorporation into new virus particles is essential for HIV-1 infectivity [45]. Experimental studies showed that cyclophilin inhibitors v.g. CyA exert and inhibitory effect on SARS-CoV through the calcineurin pathway inhibition that, at the same time, plays an important role in the SARS-CoV virus replication. In addition, CyA and tacrolimus down-modulated the calcineurin/Nuclear Factor of Activated T cells inflammatory pathway induced by SARS-CoV [46,47]. In this way, pathogenic similarities between severe pulmonary COVID-19 and the anti-melanoma differentiation-associated gene 5-positive (anti-MDA-5) antiviral dermatomyositis-associated rapidly progressive interstitial lung disease could be taken in account. Interestingly, MDAS cell sensor may be activated by viruses [48]. CyA or tacrolimus with or without intravenous immunoglobulins (IVIG) is a mainstay of pharmacologic treatment of the anti-MDAS syndrome [49]. In addition, cases of anti-MDAS syndrome complicated by haemophagocytic syndrome have been described [50]. Thus, according to the antiviral and anti-inflammatory properties of calcineurin inhibitors, CyA and tacrolimus could be potential effective drugs for treating the severe forms of COVID-19.

4.5. Other cytokine-targeted therapy

In the same line, other targets could be therapeutic options such as IL-37 and IL-38 [51]. IL-37 inhibits inflammation by acting on IL-18Ralpha receptor, on mTOR and increasing the adenosine monophosphate (AMP) kinase. IL-38 is also a suppressor cytokine which inhibits IL-1b and other pro-inflammatory IL-family members [51]. Treatment of WT mice with recombinant human IL-37 has been shown to be protective in several models of inflammation and injury. These cytokines might represent novel therapeutic targets in patients with systemic inflammatory syndromes.

4.6. Janus kinase pathway (JAK) inhibition

JAK inhibition could affect both inflammation and cellular viral entry in COVID-19. Therefore, Richardson et al. reported that baricitinib could be a potential treatment for acute respiratory disease related to SARS-CoV-2 infection [52]. The Janus kinase 1/2 inhibitor ruxolitinib, currently FDA approved in the USA for the treatment of primary myelofibrosis, polycythaemia vera and rheumatoid arthritis, has been examined in a murine model of HPS. Mice with the manifestations of HPS were treated with ruxolitinib, with improvement in manifestations and rapid decrease in serum IL-6 and TNF-α levels. Such positive results of an off-the-shelf, currently available agent are encouraging because clinical trials could readily be undertaken in humans to treat autoimmune or inflammatory-based disorders [53]. Thus, a clinical trial with ruxolitinib in patients with SARS-CoV-2/COVID-19 has been started with encouraging preliminary results. (Capoachianii E, et al.: unpublished results).

4.7. Intravenous immunoglobulins / Hyperimmune immunoglobulin

High doses of intravenous immunoglobulins (IVIG) exert anti-inflammatory and immunomodulating effects. Applications involving immunoglobulin have expanded to include treatment for immunodeficiency diseases, immune thrombocytopenia (ITP), Kawasaki disease, neurologic disorders, SLE and other severe or refractory autoimmune diseases [54]. Among the multiple effects on the innate and adaptive immune pathways related to IVIG, doses >0,5 g per kg weight/day can interrupt the storm of inflammatory cytokines caused by different stimuli. Although preliminary studies have shown efficacy of the IVIG in the treatment of patients with severe inflammatory complaints related to influenza [52] and SARS-CoV [55] infections, we need more clinical data of COVID-19 patients as evidence [56]. Currently, a randomised controlled clinical trial of IVIG in patients with severe SARS-CoV-2 infection has been initiated (Clinical Trial.gov: NCT 04261426). We want to alert on the two potential and severe IVIG adverse effects which could have a negative survival impact on patients with severe COVID-19: a/ the transfusion (immunoglobulin)-related acute lung injury (TRALI), that may be a serious immunoglobulin transfusion-related adverse effect with high mortality, manifests with acute respiratory distress syndrome within 6 h of perfusion [57]. TRALI is an immune-mediated process and the neutrophil-priming hypothesis have been proposed as possible mechanisms [58,59]; b/ thrombotic events related to IVIG treatment with an estimated incidence of 1–16.9% [57]. According to the doubtful effectiveness of IVIG treatment in patients with SARS-CoV and the risk of severe lung injury and thrombosis [60], we think the IVIG option should be carefully analyzed before its use in severe COVID-19 patients. In addition, the convalescent plasma (CP) and hyperimmune immunoglobulin (HIVIG) – neutralising antibodies - have been tried for the treatment of severe acute respiratory syndrome of viral etiology, including MERS-CoV and SARS-CoV-2 infection. Although preliminary reports have shown that CP/HIVIG are able to reduce the mortality, especially when administered early after symptoms onset, the real effectiveness is controversial, and this therapy should be evaluated within the context of a well-designed clinical trials [61–64].

4.8. Anticoagulants: heparin and fondaparinux

Severe SARS2-CoV-2 as well as other infections are associated with clot pathway hyperactivity, probably related to pro-inflammatory state. High levels of D-dimer, which is indicative of the activation of the coagulation and/or thrombosis pathways as well as the risk of suffering venous or pulmonary thromboembolism (PTE), are found high in COVID-19 hospitalised patients. In addition, high levels of D-dimer are related with poor-outcomes and high mortality rate [65–67]. Although D-dimer levels are elevated in most patients with blood clots, D-dimer levels also are elevated in many other disorders including infection. In any event, multiple pulmonary embolus has also been observed in these patients. [68,69]. Moreover, it has been observed that COVID-19 patients with severe type may develop disseminated intravascular coagulation (DIC), PTE and arterial thrombosis [Esteve-Valverde E, et al.: unpublished data], in similar way that occurred is SARS-CoV [67]. Furthermore, different diagnostic approaches have been proposed in COVID patients with clinical suspicion of PTE [70]. Finally, data obtained from autopsies of 50 COVID-19 patients showed microthrombosis and sometimes thrombus affecting large pulmonary arteries even in the superior cave vein and right auricula. [Gianattì&Sonzogni: unpublished results].
results]. Interestingly histologic data such as alveolar and interstitial inflammation extends to the closely juxtaposed pulmonary vasculature and the normal circulatory fibrinogen levels and regional fibrinolysis with elevated D-dimer formation seen in early COVID-19 pneumonia are not a features of typical acute onset MAS/HPS [17]. This hyper-inflammatory intra-pulmonary inflammation might influence a propensity toward severe local vascular dysfunction including microthrombosis and haemorrhage resulting in a lung centric pulmonary intravascular coagulopathy (PIC) presentation rather than a DIC presentation [7].

Anticoagulation therapy is recommended for COVID-19 patients when high D-Dimer levels are detected, except for patients in whom anticoagulants are contraindicated [71].

Tang et al. [72] reported a major improvement of clot activation markers and a reduction of 28-days mortality when COVID-19 patients were treated with heparin. The recommended dose of low-molecular-weight heparin (LMWH) is 100 U per kg weight per 12 h by subcutaneous injection at least 5 days. Clinicians should closely monitor the laboratory values of patients to be alert for side effects after anticoagulant treatment. In addition, heparin exerts other pharmacological effects beyond its antithrombotic properties. Furthermore, a large body of evidence supports the concept that heparin has anti-inflammatory and immune-modulating properties. LMWH promotes survival of human endothelial cells undergoing apoptosis in response to TNF-α. Heparins are able to bind anionic molecules, such as aPL, and block complement pathway activation [73–75]. Other anti-inflammatory effects of LMWH have been postulated to be specifically TNF-α-mediated [76]. In patients with heparin allergy, fondaparinux is a good option. Fondaparinux is a synthetic pentasaccharide whose antithrombotic activity is the result of anti-thrombin-mediated selective inhibition of Factor Xa [FXa]. Neutralization of FXa interrupts the blood coagulation cascade and thus inhibits thrombin formation and further thrombus development [77]. In animal models, fondaparinux is able to prevent endothelial damage, and to bind anionic molecules such as β2GP-I and β2GP-I/anti-β2GP-I complexes [78]. Furthermore, Amara et al. [79] reported the capability of fondaparinux to block FXa-C3 cleavage, and probably further delivery of C3a and C5a. In addition, diverse virus infections, SARS-CoV and SARS-CoV-2 included, appear to be associated with an antiphospholipid antibody positivity with potential pathogenic effects [80], [81] and Esteve-Valverde et al.: TRAASVIR study: unpublished results).

Thus with the anticoagulant therapy we could kill two birds with one stone: to prevent thrombosis and to down-regulate the pro-inflammatory pathways. Nevertheless, only with clinical trials we will be able to solve this conundrum.

4.9. Glucocorticoids

Glucocorticoids (GCS) exert inhibitory effects on a broad range of innate and adaptive immune responses. Because of their inhibitory effects on multiple types of immune cells, GCS are remarkably efficacious in managing many of the acute disease manifestations of inflammatory and autoimmune disorders [82]. The anti-inflammatory and immunosuppressive effects of GCS rely on three main mechanisms that include, a/ direct effects on gene expression by the binding of glucocorticoid receptors to glucocorticoid-responsive elements, b/ indirect effects on gene expression through the interactions of glucocorticoid receptors with other transcription factors i.e., NF-κB and activator protein 1, and c/ glucocorticoid receptor-mediated effects on second-messenger cascades [83]. GCS have been used with different success in life-threatening conditions such as CID, sepsis and acute distress respiratory syndrome (ADRS) [84–86]. By its clinical similarity, GCS are currently empirically used in some hospitals in the treatment severe COVID –19 patients, and different therapeutic local guidelines have included them [87]. However, existing evidence is inconclusive or does not support for GCS treatment of COVID-19 patients to date [88–92].

Patients with severe COVID-19 infection are at risk of acute respiratory distress syndrome and death. Angiotensin-converting enzyme-2 (ACE2) is a homologue of ACE, and functions as a negative regulator of the renin-angiotensin system and it is expressed in the human lungs [94]. ACE-2 is also present in heart tissue. In addition, angiotensin-converting enzyme II is a key molecule involved in the development and progression of acute lung injury [95]. It is known that ACE-2 is a functional receptor for the SARS-coronavirus, SARS-CoV-2 included [96]. SARS-CoV-2 infects ACE2+ cells in the oral mucosa and lungs, including ACE-2 cells in the alveoli [97]. Thus, SARS-CoV-2 induces direct lung injury by involving ACE enzyme, which contributes to diffuse alveolar damage, and high levels of ACE2 can protect against ARDS [98]. It is worthy of mention that higher levels of ACE-2 and ACE2+ cells, higher regenerative capacity and a strong immune response lead to an effective viral clearance [99]. With age or when certain comorbidities are present, such as hypertension or diabetes, the ACE-2 levels decrease with subsequently slower in viral clearance, sustained ACE cell injury, lung inflammation and risk of precipitating into ARDS [97,100]. Numerous agents have been shown to modulate and upregulated ACE2 expression, including angiotensin peptides and some other peptide and steroid hormones [98]. Interestingly, ACE inhibitors and angiotensin II receptor blockers increase ACE2 levels. This fact could partially explain the relationship between increased fatality rate of COVID-19 in patients with cardiovascular diseases, including hypertension [101]. Currently, a clinical trial (Clinical Trials.gov: NCT04287686) using recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19 is ongoing.

Statins induced potent inhibition via protein geranyl geranylation of pro-inflammatory cytokine production (TNF-α, IL-10, IL-6 and IL-8) in mononuclear, synovial and endothelial cells. Statins also inhibit T-cell activation and proliferation, leading to the immunomodulatory effects. Furthermore, statins inhibit MHC-II expression on endothelial cells and monocyte-macrophages via inhibition of the promoter IV of the transactivator and thereby repress MHC-II mediated T-cell activation [102,103]. In 2014, it was suggested that statins might be used to treat patients with Ebola virus disease [104]. A supply of a generic statin and a generic angiotensin receptor blocker [ARB] was sent to Sierra Leone. Experimental studies had shown that both drugs improved outcomes in experimental acute lung injury/ARDS models [105,106]. A far as we know no data on use of these drugs on SARS-2-CoV-19 patients have been published so far. Clinical trials are needed to determine whether this drug combination might be used to treat patients with severe COVID-19 [107].
5. Infectious agents, cytokines and induction of autoimmunity

It is already known, even in individuals with appropriate genetic background, that environmental factors participate to trigger autoimmune disease (AD). It is also possible that infections accelerate an already established subclinical autoimmune disorder [108]. Diverse mechanisms have been proposed i.e. molecular mimicry (cross-reactivity between the microorganisms and host tissue), the production of superantigens, deviation of the balance between T-helper subsets toward Th1 or increase Th1/Th2/ regulatory T cells (Treg) ratios (loss of active cytokine regulation) and the apparition of self-neoantigens [108,109]. Thus, a variety of hypotheses have been put forward to explain the onset of AD, but all of them are dependent of the auto-reactivity of T and/or B lymphocytes that have escaped of the regulatory controls. The increased levels of Th1-derived cytokines, mainly IL-1, IL-6, TNF-α and IFN-γ may be the effects of autoreactivity but, in turn, may facilitate the loss of immune control and eventually the apparition of AD [109]. As an example, IL-6, a proinflammatory cytokine, also affects T cells. IL-6 is one of the factors that determine how naïve cells turn, may facilitate the loss of immune control and eventually the apparition of AD [109].

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6. Conclusions

COVID-19 is a primarily respiratory tract infection with different forms of clinical manifestations. While most infected people only develop mild illness, approximately 15–20% develop severe disease that requires hospitalization and 5% require admission to an intensive care unit. In severe cases, COVID-19 with MAS occurs in patients with ARDS, sepsis and septic shock, and ultimately, multiorgan failure and death, linked to sustained IL-6 and IL-1 elevation.

While mild clinical forms only require symptomatic management, in moderate-severe forms in-hospital surveillance with general measures plus antiviruses and/or HCQ administration is necessary. However, in more severe and life-threatening cases, a high intensity pharmacological treatment is recommended. The pathogenesis of the acute pulmonary injury related to COVID-19 is very similar that occur in other disorders that induce high hyperinflammatory state with a release of high amounts of pro-inflammatory cytokine mainly, IL-1, IL-2, IL-6 and TNF-α. A pro-thrombotic status appears later. Thus, drugs that usually serve to treat rheumatic or autoimmune syndromes may play a major role in this setting. To date, only HCQ has proved to be useful for the treatment of severe cases of pneumonia related to COVID-19. Attention should be paid with cardiac side effects when high HCQ doses are administered in COVID patients. However, pre-clinical and few clinical made in patients with severe COVID-19 show that intense immunosuppressive drugs improve clinical severity and reduce the mortality rate. Thus, antiviral and supportive measures apart, the combination of high HCQ doses plus immunomodulatory agents such as tocilizumab, cyclosporine or others are warranted mainly in the context of clinical trials, in order to demonstrate a possible benefit in those severe COVID-19 patients.

If this schema fails, IVIG or short course of GCs can be tried. High prophylactic or full heparin should be administered according to D-dimer levels. The role played by JAK-inhibitors, statins, or ACE-2-agonist is currently unknown. In addition, the effectiveness of the transfusion of hyperimmune plasma – neutralising antibodies -obtained of cured COVID-19 patients is speculative. Attention should be paid when neutralising antibodies are used, since the effectiveness or deleterious effect can be time-dependent. Only randomised clinical trials although difficult to perform in this context, would be the pathway to exit from this labyrinth and allow the scientific community to affront

Table 4
Recommended doses of drugs potentially useful for treating severe “cytokine storm” associated with COVID-19:

| Drug                          | Recommended doses                                      | Notes |
|-------------------------------|--------------------------------------------------------|-------|
| Hydroxychloroquine phosphate | 400 mg tablets: 1 tablet q12 as loading dose, followed by 200 mg tablets, 1 tablet q12, during 10 days, or 1 and half tablet q12 during 7–10 days. |       |
|                              | Alternatively: Chloroquine phosphate 250 mg tablets, 2 tablet q12, during 10 days. |       |
|                               | Heparin: LMWH at high prophylactic dose, i.e. enoxaparin 1 mg q24. Consider full anticoagulant dose if D-dimer >1500–3000 |       |
|                               | Tocilizumab*: 8 mg/kg (maximum 800 mg/dose), single dose intravenously (1-h infusion); in absence or with poor clinical improvement a second dose should be administered after 8–12 h (maximum recommended doses: 3) |       |
|                               | IVIG*: 0.5–1.0 g/Kg (maximum doses: 2 g/kg) |       |
|                               | Methyl-prednisolone*: 1 g/Kg q24 (IV) x 3 days, followed by 0.5 mg/Kg q24 x 3 days. Alternatively: 250 mg q 24 × 3 d (IV) |       |

* Although lopinavir/ritonavir appears not to be effective, preliminary results with Remdesivir showed positive effect in 68% of cases [121].
# In cases with plasmatic IL-6 levels ≥ 40 pg/mL.
§: Some authors recommended doses of 0.5–0.5 g/Kg q24 h per 3 days [122].
¶: The is no agreement in its usual use.
 Cyclosporin A, Anakinra and Canakinumab could empirically be administered if tocilizumab fail or it cannot be used.
•: See references: [82, 83, 90, 93, 117, 118, 119, 120]. Standard of care includes: antiviral plus azithromycin plus hydroxychloroquine.
this colossal challenge. In these lines, different trials involving hydroxychloroquine, tocilizumab, sarilumab, anakinra, immunoglobulins, plasma hyperimmune, cyclosporine A and ruxolitinib are ongoing or just started. A possible therapeutic approach can be seen at Table 4. Thus, we face a double edge sword when considering treatment with immunosuppressive drugs in those patients. One the one hand it may be useful to control the inflammatory response that certainly may be harmful for the patient, and on the other side, it could favour the virus shedding. However, taking into account the poor outcomes of these patients, and meanwhile we are waiting for more results based on clinical trials, our feeling is that immunosuppressors play a major role and that as earlier the immunosuppressive treatment is started the less complications and deaths there will be. The future will show us the correct answer.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

The author also state that they do not have any commercial or any other type of interest that may have influenced the drawing up and the results of this paper.

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