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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-threating 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; IFNγ, Interferon gamma; IL, Interleukin; JAK, Janus-Kinase family of enzymes (JAK1, JAK2, JAK3, TYK2); IVIG, Intravenous immunoglobulins; MDA5, 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-$_{\kappa}\beta$, Nuclear Factor-$_{\kappa}\beta$; 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; TRAASVIR, 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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Table 1
World Health Organization. Clinical management of severe acute respiratory infection [SARI] when COVID-19 disease is suspected Interim guidance 13 March 2020

Mild ARDS: 200 mmHg < PaO2/FiO2 a ≤ 300 mmHg [with PEEP or CPAP ≥5 cmH2O, or non-ventilated] • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg [with PEEP ≥5 cmH2O, or non-ventilated] • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg [with PEEP ≥5 cmH2O, or non-ventilated] • When PaO2 is not available, SpO2/FiO2 ≤ 315 suggests ARDS [including in non-ventilated patients]. Oxygenation impairment in children: note OI = Oxygenation Index and OSI = Oxygenation Index using SpO2. Use PaO2-based metric when available. If PaO2 not available, wean FiO2 to maintain SpO2 ≤ 97% to calculate OSI or SpO2/FiO2 ratio: • Bilevel [NIV or CPAP] ≥ 5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264 • Mild ARDS [invasively ventilated]: 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS [invasively ventilated]: 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 Severe ARDS [invasively ventilated]: OI ≥ 16 or OSI ≥ 12.3. Sepsis: Adults: life-threatening organ dysfunction caused by a dysregulated host response

1. Introduction

Severe Acute Respiratory Syndrome related to Coronavirus-2 (SARS-CoV-2), is the infectious agent causing coronavirus disease 2019 (COVID-19) may cause systemic inflammatory response with severe acute respiratory syndrome [1,2] (Table 1). It emerged as an outbreak in early December 2019 in Wuhan, China [3] and from March 13 is a pandemic according to WHO criterion, carrying a mortality of approximately 3,7% [4]. Some previous pathological conditions of the patients may have a major impact on survival [Table 2]. We must bear in mind that currently, no specific antiviral treatment is available for COVID-19, and therefore further research into the pathogenesis of human coronavirus infection is imperative for identifying appropriate therapeutic targets. Right from the first time that the outbreak appeared in China, the importance of immunomodulation in the clinical progression of the infection was described [5]. Given the severity of the immunological picture it has been suggested a series of etiopathogeneic mechanisms that are close to the ones involved in other immunomediated disorders.

2. SARS-CoV-2, cytokine storm and hyperinflammatory syndrome

One of the principal candidates to explain the catastrophic evolution of some people infected with SARS-CoV-2 is the haemophagocytic syndrome (HPS) also named haemophagocytic lymphohistiocytosis [6] and similarly, the macrophage activation syndrome (MAS), a subtype of HPS in which the syndrome develops in the background of autoimmune disease, particularly in adults, Still's disease, systemic lupus erythematosus (SLE) and vasculitis [6,7]. HPS is a life-threatening disorder characterized by unbridled activation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages resulting in hypercytokinemia and immunomediated injury of multiple organs or systems [6]. Clinical and laboratory manifestations include fever, splenomegaly, neurologic dysfunction, coagulopathy, liver dysfunction, cytopenias, pulmonary involvement, hypertriglyceridemia, hyperferritinemia, hemophagocytosis, and diminished NK cell activity [6]. According to Prof. Shoenfeld [7], two more syndromes may present with similar severe clinical pictures and hyperferritinaemia: the catastrophic antiphospholipid syndrome and the adverse reaction to the biological compound anti-CD-28 [7–9]. Interestingly, these syndromes share similar clinical picture that severe COVID-19. Additionally, it has also been suggested to test for soluble CD-163 (sCD-163), which represents macrophage activation, the level of which was found to increase in MAS and to parallel the ferritin level [10]. Whether the hyperferritinaemia is just an epiphenomenon that can help us for diagnostic, or the ferritin is “per se” able to perpetuate the inflammatory loop is speculative. However, Ruscitti and Shoenfeld [11] have found that the H-chain of the ferritin is able to activate macrophages to increase the secretion of inflammatory cytokines and eventually, ferritin. This pathway would be common to all hyperferritinaemic syndromes, COVID-19 included [11]. HPS and MAS could be triggered by an excessive immune response to a viral infection [6,12,13]. Different virus has been related to HPS, mainly Epstein-Barr, cytomegalovirus, other herpes viruses, and human immunodeficiency virus [6,14]. Pathology similar to HPS was reported in both SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV infections [15,16]., and has been suggested in COVID-19 [5]. However, McGonagle et al [17] hypothesised that MAS related to severe SARS-CoV-2 infection has distinctive characteristics than classical MAS/HPS. They argue that, at the beginning, the hyper-inflammatory reaction appears to be more confined to the lungs based on histopathological findings (see below). In addition, COVID-19 patients usually do not present lymphadenopathy or splenomegaly. Furthermore, pulmonary hemophagocytosis has not yet been reported in COVID-19 associated pneumonia [18].

Table 2
Variables related to high risk to develop severe COVID*

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

* The role played by obesity, smoking, asthma, hyperferritinaemia and high IL-6 levels as risk factors for severe COVID are not clearly stablished to date.

Since HPS and MAS are a hyperinflammatory syndrome, an extreme elevation in pro-inflammatory cytokine and acute phase reactants levels are observed (the exception to this is the erythrocyte sedimentation rate, which may be low due to hypofibrinogenaemia), among them: IL-1β, IL-2, IL-6, IL-7, G-CSF1, IP-10, MCP-1α, MIP-1α, TNF-α, and sIL2R [6,19,20]. A hyperinflammatory profile that resembles HPS is described in clinical features of hospitalised COVID-19 patients, [7,18]. In addition, the binding of SARS-CoV-19 to the Toll Like Receptor (TLR) will be followed by the release of pro-IL-1b cleaved by caspase-1, will induce inflammasome and IL-1b activation, which is a mediator of lung inflammation. Clinical observations indicate that few patients' health worst at 6–8 days after infection. According to theory of disease tolerance the most severe cases of COVID-19 could be in part due to an uncontrolled immune response to SARS-CoV-2 infection [21]. The reduction of this inflammatory immune response could be considered as a potential therapeutic target against severe COVID-19. Consequently, the proposal to treat severe COVID-19 with immunomodulatory therapy as it is done in HPS is likely to be beneficial to tackle hyperinflammation and eventually to ameliorate the severe clinical syndrome [5,22]. Theoretically, corticosteroid treatment could have a role to suppress systemic and lung inflammation related to COVID-19. Nevertheless, the therapeutic use of corticosteroids that has excellent pharmacological effects to suppress exuberant and dysfunctional systematic inflammation is still controversial [22–25]. Thus, the current National Health Council (NHC) guideline emphasizes that the routine use of systematic corticosteroids is not recommended unless indicated for another reason. In this line, there was no available data showing that the patients benefited from corticosteroid treatment in SARS-CoV or MERS infection, which might be attributed to the suppression of immune response and virus clearance [23]. In addition, the use of the sera of immunised people for treating severe case of COVID-19 has also been suggested. However, some concerns arise on this proposal. In relation with the discrepancy on the severity of cases observed with current COVID-19, one possible answer could be the role played by antibody dependent enhancement (ADE) of SARS-CoV-2 [26]. Immunization 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 similarity for COVID-19, to include drugs that block IL-1, IL-2, IL-6, IL-18, and IFNγ [28]. In addition, other drugs capable to block other inflammatory pathways such as anti-malarials, baricitinib or ruxolitinib [Janus-kinase inhibitors] should also be considered. (Table 3).

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”, “antimalarials”,” 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 retrieved and included (CDC, Australian, WHO, Spanish and Italian). The authors reviewed the selected manuscripts and finally the most appropriated were included for this review.

Table 3
List of drugs potentially useful for treating severe “cytokine storm” associated with COVID-19*

Antimalarials: hydroxychloroquine and chloroquine
IL-6 blockers: Tocilizumab and Sarilumab
Calcineurin inhibitors: Cyclosporine A and Tacrolimus
IL-1 blocker: Anakinra, Canakinumab
Heparins: low-molecular-weight and unfractionated heparin
Intravenous immunoglobulins (IVIG)
Hiperimmune immunoglobulins (neutralising antibodies)
JAK inhibitors: Ruloxitinib, Bariticinib
Corticosteroids (methylprednisolone)
Statins
Recombinant human angiotensin-converting enzyme 2 (rhACE2)

* Other procedures such as CytoSorb® adsorber, that can lead to a reduction of the circulating pro-inflammatory (and anti-inflammatory) cytokines could improve the course of the disease and the outcome of the patients when used together with other therapy. Currently there is a trial to study the efficacy of this procedure (University Hospital Freiburg, Germany NCT 04324528).

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-2-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 fibromyxoid 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 refractary 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 downmodulated the calcineurin/Nuclear Factor of activated-T cells inflammatory pathway induced by SARS- [46,47]. In this way, pathogenic similarities between severe pulmonary COVID-19 and the anti-melanoma differentiation-associated gene 5-positive (anti-MDA-5) amyotrophic dermatomyositis-associated rapidly progressive interstitial lung disease could be taken in account. Interestingly, MDA5 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-MDA5 syndrome [49]. In addition, cases of anti-MDA5 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-18Ra 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, polycythemia 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. (Capoachiani 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 microthombosis and sometimes thrombus affecting large pulmonary arteries even in the superior cava vein and right auricula. [Gianatti&Sonzogni: unpublished 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 hyperinflammatory 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-$_{\mathrm{k}}$β 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]. Prudent use with low-to-moderate doses and short courses of treatment could be advised in selected cases [87,92,93]. According to Cochrane review [88], the WHO recommendations [91] and expert consensus statement from Chinese Thoracic Society [90], some basic principles should be followed when using corticosteroids in severe COVID-19 patients: [a] benefits and risks should be carefully weighed before using GCS [b] GCS should be used carefully in critically ill patients with SARS-CoV-2 pneumonia; [c] for patients with hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic diseases, further use of corticosteroids should be cautious and [d] dosage should be low to moderate (≤ 0.5–1 mg/ kg daily of methylprednisolone or equivalent) and duration should be short (≤7 days). Thus, high doses or pulses of GCS are not recommended. Furthermore, WHO [82] and CDC [93] recommend that corticosteroids not to be routinely used in patients with COVID-19 for treatment of viral pneumonia or ARDS unless indicated for another reason. Finally, in cases of life-threatening septic COVID-19 patients, clinicians who consider to add corticosteroids to “goal standard” treatment should balance the potential small reduction in mortality with potential effects of prolonged coronavirus shedding.

4.10. Other possible complementary nonviral drugs to be used: ACE agonists and statins

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 stablished 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 autoreactivity 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 $CD4^+$ T cells differentiate into particular effector T cell subsets. IL-6 in combination with transforming growth factor-beta (TGF)-β preferentially induces differentiation into Th17 cells, whereas IL-6 inhibits TGFβ-induced Treg development. The resultant predominance of Th17 cells over Treg cells may be responsible for the breakdown of immunological tolerance, and may therefore be pathologically involved in the development of AD [110]. Deregulated excessive IL-6 synthesis during this protective process or persistent IL-6 production leads to the development of a severe acute life-threatening complication, the so-called cytokine storm or AD respectively [111]. HLA-class II and particularly HLA-DR are expressed constitutively mainly by antigen presenting cells (APC), and B cells and by some activated T cells. Their expression is essential for starting the adaptive immune response and help to clear infections through it. Furthermore, HLA-DR overexpression on these cells or, the apparition "de novo" class-II-DR complex in other cells that usually lack HLA-DR, may facilitate its recognition as non-self cells and eventually, cause AD. IFN-γ leads to HLA-DR gene expression concomitant with inflammatory cytokine genes such as IL-1 beta TNF-α, and IL-6 in vitro [112]. This MHC class II upregulation increases MHC-restricted antigen presentation and adaptive immune response. In addition, IFN-γ can inhibit the differentiation and proliferation of Th2 cells, and the sustained response of Th1 cells is involved in the occurrence and development of AD. Many infectious agents like Epstein-Barr virus, CMV and parvovirus, among others, have been implicated in the pathogenesis of certain AD v.g. rheumatoid arthritis (RA), SLE and psoriasis. Although the exact mechanism by which pathogens causes pathology is unknown, presence of class II molecules is mandatory [108,113]. Thus, certain viral infections, coronavirus among them, are able to induce a high amount of proinflammatory cytokines in predisposed host, that eventually may cause hyperferritinaemic syndrome (haemophagocityc/MAS-like syndrome) [7,108]. In addition, the increase of Th1 and Th17-derived cytokines will induce, proinflammatory milieu apart, a decrease in IL-4, IL-10 and TGF-β with a subsequent decrease in total and functional Tregs (CD4 + CD25 and CD4 + CD25 + FoxP3+) that limits the major arm to control self-tolerance. Another issue that deserves some consideration is the role of Treg cells in the severity of the COVID-19. It has been reported that severe cases present a lower proportion of naïve Tregs but a higher of memory Tregs which in turn, although not demonstrated, probably may play a role leading to a high intensity autoimmune response [114]. Furthermore, IFN-γ is able to increase the expression of the class-II-DR + molecules in immune cells and to induce their expression in non-immune cells, thereby facilitating the apparition of auto-neoantigens, autoimmune response and eventually AD [115]. In conclusion, combination of the possible molecular mimicry (viral particles) plus cytokine imbalance [116] plus Treg cells decrease and class-II-DR molecules overexpression, are the "perfect storm" for a loss of self-tolerance, autoimmune dysfunction and eventually AD.

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 antivirus and/or HCQ administration is necessary. However, in more severe and life-threating 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, antivirals 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 dose 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*.

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 (maxium doses: 2 g/kg)
Methtyl-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)

ϕ 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 leves ≥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: antivirals[ϕ] plus azithromycin plus hydroxychloroquine.

this colossal challenge. In these lines, different trials involving hydroxychloroquine, tocilizumab, sarilumab, anakinra, immunoglobulins, plasma hyperimmune, cyclosporine A and ruloxitinib 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 in 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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