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COVID-19-Driven Immunoparalysis and Cytokine Storm: Can Hematologists Contribute to the Battle?

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Abstract

COVID-19 pandemia is a major health emergency causing hundreds of deaths worldwide. The high reported morbidity has been related to derangement of the immune system, cytokine overproduction and endothelial dysfunction. Several drugs currently marketed for blood disorders are being tested for potential clinical benefit in patients with COVID-19 and hematologists are valuable partners for multidisciplinary research projects assessing host-targeted therapies. This review attempts to highlight the pathogenesis of lymphopenia in COVID-19 disease and the possible treatment pathways. While discussing the pattern of cytokine hyperproduction, we also focused on anti-cytokine drugs being tested for COVID-19 disease but currently prescribed for blood disorders.

Keywords: COVID-19; SARS-CoV; Lymphopenia; IL-6; GM-CSF; Tocilizumab; Baricitinib; Ruxolitinib; Siltuximab; Sarilumab

Abbreviations: ABL: Abelson Murine Leukemia; ACE: Angiotensin Converting Enzyme; AKT: Protein Kinase B; ARDS: Acute Respiratory Distress Syndrome; AT1: Angiotensin Receptor 1; AUC: Area Under The Curve; CAR-T: Chimeric Antigen Receptor-T Cell; CCR C-C: Motif Chemokine Receptor; COPD: Chronic Obstructive Pulmonary Disease; CoV: Coronavirus; COVID-19: New Coronavirus Related Disease; CXCL C-X-C: Motif Ligand; CXCR C-X-C: Motif Chemokine Receptor; DAMP: Danger-Associated Molecular Patterns; EMA: European Medicines Agency; EPC Endothelial Progenitor Cells; G-CSF: Granulocyte Colony Stimulating Factor; GM-CSF: Granulocyte Monocyte Colony Stimulating Factor; GVHD: Graft Versus Host Disease; HCV: Hepatitis C Virus; HIF: Hypoxia Inducible Factor; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; ICAM-1: Intercellular Adhesion Molecule-1; ICU: Intensive Care Unit; IDO: Indoleamine-2,3-Dioxygenase(IDO)- IKK IkB kinase; IL: Interleukin; IP10: Interferon-Gamma-Inducible Protein 10; JAK: Janus Kinase; MAPK: Mitogen-Activated Protein Kinase; MCP1: Monocyte Chemoattractant Protein 1; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; MIP1A: Macrophage Inflammatory Protein 1; mTOR: Mammalian Target of Rapamycin; NF-kB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; NK: Natural Killer; P2Y12: Adenosine Diphosphate Receptor; PD-1: Programmed Cell Death Protein; PI3K: Phosphatidylinositol 2-Kinase; RNA: Ribonucleic Acid; rTPA: Recombinant Tissue Plasminogen Activator; SARS: Severe Acute Respiratory Syndrome; SARS-CoV-2: SARS-Related New Coronavirus; SOCS: Suppressor of Cytokine Signaling; TIM-3: T-Cell Immunoglobulin Mucin-3; TNF: Tumor Necrosis Factor; Treg regulatory T-lymphocytes; VCAM: Vascular Cell Adhesion Molecule; VEGF: Vascular Endothelial Growth Factor 4.

Introduction

Humans are highly susceptible to infection with respiratory viruses including respiratory syncytial virus, influenza virus, human metapneumovirus, rhinovirus, coronavirus (CoV), and parainfluenza virus. While some viruses simply cause symptoms of common cold, many respiratory viruses induce severe bronchiolitis, pneumonia, and even death following infection. Coronaviruses, including SARS and MERS, caused two major pandemics in the last

two decades. Recently, a severe respiratory syndrome caused by a new coronavirus (SARS-CoV-2) has seriously endangered China, Italy and several other countries [1]. A fatality rate ranging from 2% to 10% has been reported for SARS-CoV-2 related coronavirus disease 2019 (COVID-19) [2,3]. Old age (Odds Ratio 1.10 per year increase), high Sequential Organ Failure Assessment (SOFA) (Odds Ratio 5.65) and comorbidity were related to higher fatality rates.4 In particular, non-survivors had both respiratory failure and sepsis hallmarks [4].

Several antiviral agents are currently being tested for COVID-19 treatment: remdesivir, arbidol, ribavirin, lopinavir/ritonavir, aerosolized interferon-alpha, cloroquine, favipiravir (RNA-dependent RNA polymerase inhibitor), darunavir (HIV-1 protease inhibitor) [5]. Nevertheless, patients with severe COVID-19 need powerful symptomatic treatments and immune rescue while attempting to reduce the viral load, since disease severity is believed to be due to viral evasion of host immune response, virus-induced cytopathic effects and aberrant host cytokine storm. This review summarizes the available evidence on the multiple derangements caused by SARS-CoV-2 infection and the potential role of off-label targeted biologic treatments.

Innate and Adaptive Immune Response to Respiratory Viruses

T-Helper and T-Regs Responses to Respiratory Viruses

Respiratory viruses initially target lung epithelial cells and/or alveolar macrophages. Innate immunity is thus activated to inhibit viral replication and recruit adaptive immune response by chemokines like interferon [6]. Upon chemokine recruitment, helper T cells migrate into the airways and lungs and achieve an efficient clearance of the virus, which is the typical Th1-mediated response to influenza virus. However, helper T cells sometimes exert a pathogenic effect, such as Th2 lymphocytes in infections with syncytial virus and rhinovirus. A reduced mortality has been observed in CoV mice models upon depletion of alveolar macrophages, with consequent reduced migration of virus-specific CD4+ T cells and increased Tregs in the lung airways [7]. Prevention of pathogenic effect also seems to be the aim of excessive inhibition of T-cell responses by Tregs observed in many respiratory viral infections [8].

Immunosenescence

Whereas younger individuals adequately respond to CoV, aged individuals show much less efficient responses. Age-related decrease of innate immune defense against SARS-CoV has not only been attributed to a higher expression of secretory phospholipase A2 in CD11c+ lung cells, which prevents dendritic cell migration to lymph nodes and virus specific T cell response, [9] but also to a lower drive to Th2 lymphocyte differentiation by bronchial epithelial cells [9,10]. Moreover, both B and T lymphocyte counts decrease with age due to the absolute lymphocyte decline and to a percent decline of CD19+ cells [11]. In Chinese individuals, CD3+ lymphocyte count decreases from > 1500/mm3 in individuals below 40 years of age to less than 1000 in individuals over-80. A 25% decline of CD19+ lymphocytes is achieved late in time, i.e. over 70 years of age, while it is achieved at 40 years by CD8+ cells and at 50 years by overall CD3+ lymphocytes [12].

Lymphopenia is a relevant age-related hallmark, since in a population-based study of 98,344 Danish individuals, lymphocyte counts lower than 1100*10^6/l increased the hazard ratios for any infection of 1.41, for sepsis of 1.51 and for infection-related death of 1.70, after adjusting for several covariates [13]. Relative lymphopenia was also a strong prognostic factor in elderly people with COPD and inversely correlated with comorbidity and survival [14,15]. Immunosenescence has been attributed to thymic involution, chronic inflammation, hypovitaminosis D, [16] and upregulation of immune checkpoint inhibitors in lymphocytes [16]. While vitamin D deficiency has been reckoned to be partially responsible for age-related lymphopenia, [17] calcitriol protects CD4 lymphocyte from HIV infection [18] and in vivo supplementation increases Tregs in healthy volunteers [19]. A recent meta-analysis has stated a strong correlation between vitamin D deficiency and infections and consequentclinical advantages of its supplementation onto respiratory infections [20]. However, it is mainly considered anunspecific prevention of immunosenescence rather than a potential anti-COVID-19 supportive therapy [20-23].

Mast Cells

The immune response to CoV also relies on mast cells, which are the first to respond to pathogen invasion along with dendritic and epithelial cells. Mast cells are found in environmental interfaces, such as the submucosa of the respiratory tract and the nasal cavity, typically next to blood or lymphatic vessels and nerve endings, and regulate both the innate and adaptive immune response. They contribute to inflammation by the immediate release of prostaglandins and leukotrienes and the delayed secretion of de novo synthesized cytokines (Il-1, IL-33), chemokines and growth factors that increase epithelial and endothelial cell permeability and activation state, thus attracting inflammatory cells to sites of CoV infection [24]. Excessive mast cell activation is a common feature of viral infections causing Acute Respiratory Distress Syndrome (ARDS).

Lymphopenia Secondary to Infections: Diagnostic and Prognostic Issues

Sepsis-Related Lymphopenia

A decreased lymphocyte count has been reported both in chronic viral diseases and sepsis, the latter being the first cause of lymphopenia in hospitalized patients: most septic patients present with less than 800/mm3 absolute lymphocyte count and less than 300/mm3 CD4+ lymphocytes [25]. Furthermore, lymphocyte count has a high diagnostic power for sepsis (AUC 0.971), significantly higher than procalcitonin and leukocyte count [26]. Mice sepsis models did not report a decreased number of bone marrow precursor cells, but rather a dramatic decrease in the percentage of early T lineage progenitors [27]. Bone marrow progenitors of T lymphocytes exhibited reduced homing capacity and expressed reduced mRNA levels of CCR7, CCR9 and P-selecting gp ligand-1, thus showing that emergency myelopoiesis during sepsis is mainly myeloid-directed [27].

Lymphopenia-Related Prognosis

Lymphocyte count predicts sepsis-related fatality; 28-day mortality is as high as 39% in individuals reporting lymphocytes below 760/mm3, and persistent lymphopenia for > 3 days predicts high mortality rate [26]. Multivariate analysis confirmed that lymphopenia <675 cells/mm3 or <501 cells/mm3 translated into 2.32- and 3.76-fold risk of mortality in patients with or without septic shock, respectively. However, the protective effect of lymphocytes has not been completely ascertained, since endotoxemic pulmonary dysfunction and recovery do not seem to be affected by the presence or absence of T-cells [28]. Moreover, the interplay of T-cells with neutrophils and immunoglobulins has not been fully investigated: increased immunoglobulins associated with T-cell lymphopenia in the early phases of sepsis were correlated to clinical worsening, while normal neutrophil counts (<8850 cells/mm3) in patients with septic shock translated into 3.6-fold risk of mortality [29,30].

Other Causes of Lymphopenia

Early lymphopenia occurs also during Ebola virus infection and correlates with prognosis; [31] also severe trauma, surgery and burns often cause lymphopenia, which is related to final patient outcomes [32]. Moreover, most of ICU patients exhibit lymphopenia, regardless of the nature (septic or sterile) of the initial medical condition [33]. Circulating CD3+ T cells and CD3-CD56+ NK cells are mainly concerned, while data on helper innate lymphoid cells (helper ILCs - ILC1, ILC2, and ILC3) are inconclusive. Out of 473 ICU Italian patients (277 with ventilator-associated pneumonia), lymphocyte count below 595/mm3 best discriminated 28-day and 90-day mortality: 28% vs 18% and 53% vs 34% (HR 1.41 at multivariate analysis). However, both SOFA and comorbidities correlated with more severe lymphopenia, therefore a conclusive cause or effect role for lymphopenia has not been established yet [34].

Infection-Related Lymphopenia: Pathogenesis

Sepsis-induced immunodeficiency was primarily attributed to early apoptosis of lymphoid cells, especially CD4+ circulating and resident effector cells, documented both in autopsy and in vivo studies, and induced by histones released by neutrophils under the stimulus of C5a [35]. Apoptotic cells cause a shift from pro-inflammatory to anti-inflammatory immune cytokine production (IL-10) and Th2 polarization of the immune response, as well as induction of T regs, which are predictive of fatal outcome [36]. Indeed, Tregs seem to be resistant to apoptosis, while CD4 CD28 immunocompetent lymphocytes decline, especially in elderly septic patients.

CD4+ cell death might also be the result of direct viral action: it has been related in vitro to Ebola glycoprotein, which interacts with TLR 4, inducing pro-apoptotic signals via NFkB activation [31]. A third pathogenic way of infection-induced immunodepression is viral-induced up-regulation of PD-1 expression in lymphocytes, which causes functional exhaustion, inhibition of proliferation and induction of apoptosis, as it happens during acute and chronic HIV and HCV infections [37]. Sepsis may also reduce bone marrow production of lymphocytes by a G-CSF-mediated inhibition of osteoblasts in the bone marrow niche; a subsequent reduction of the nourished common lymphoid progenitors and peripheral lymphopenia is expected [38]. Finally, a yet poorly explored pathway toward lymphopenia may be mediated by serum tryptophan, which has been reported to be greatly reduced during viral infections and protein malnutrition: such a deficiency reduces CD4+ and CD8+ lymphocytes both in blood and spleen, by an ACE2- and indoleamine-2,3-dioxygenase (IDO)-related mechanism [39].

Lymphopenia and Immunoparalysis in the Course of COVID-19 Pneumonia

Prognostic Yield of Lymphopenia

Patients with COVID-19 pneumonia rarely show leukocytosis, and their mean leukocyte count is thus 40% lower than the observed count in non-COVID-19 pneumonia [40]. In particular, 75% of COVID-19 patients show lymphopenia: lymphopenia and especially persistent lymphopenia is significantly higher in non-survivors versus survivors [4,41]. Moreover, among the clinical parameters,

lymphocyte count reported the highest inverse correlation with viral load [42]. While CD19+ count did not correlate with patient outcome, CD3+ cell count was about half as high in patients admitted to ICU, due to a more marked decrease in CD8+ cells [4,43-45]. Therefore, the newly reported clinical entity "Lymphopenic community acquired pneumonia"-a particular pneumonia characterized by dysregulated immunological response with hypercytokinemia and high mortality-seems to be the signature of severe COVID-19 infection [46-48]. Interestingly, a close interconnection between lymphopenia and endothelial dysfunction has been reported in patients with lymphopenic pneumonia and multi organ failure [47].

Pathogenesis of COVID-19 Related Lymphopenia

To explain the very low lymphocyte count observed in severe cases of COVID-19, it was hypothesized a direct cytotoxic action of the virus, [45,49] and antibody-mediated infection of lymphocytes. Antibodies directed to spike protein of SARS-Cov have been proved to inhibit viral entry in epithelial cells, but also potentiate infection of immune cells via Fcgamma receptor II and allow escaping of the endosomal/lysosomal pathway [50].

Lymphocyte exhaustion has been proposed as a third mechanism for lymphopenia, since an activated (CD69+, CD38+, CD44+) and exhausted status (co-expression of Tim-3 and PD-1) have been demonstrated in T cells of patients admitted to the ICU [51,52]. However, while down regulation of Th1- and Th2-related cytokines and receptors correlated with fatality rate in MERS-CoV, [53] through depletion of CD8+ T cellsMERS-CoV-infected mice were protected from organ damage and clinical symptoms, and in children with respiratory virus infections a higher CD8/CD4 ratio predisposed them to ARDS evolution [54,55].

Lymphopenia in Special Populations

ACE2 is an enzyme, which cleaves angiotensin II to generate angiotensin 1-7, a potent vasodilator, but it is also an important regulator of inflammatory and immune response in the lungs protecting individuals from sepsis, avian influenza and H5N1 virus [56]. SARS-CoV-2 uses ACE2 as the receptor binding domain for its spike protein, leading to ACE2 downregulation and excessive angiotensin levels, as well as lung injury by angiotensin receptor 1 (AT1)-mediated vascular permeability [57,58]. Moreover, stimulating AT1 on macrophages and Th1 lymphocytes drives their differentiation and release of IL1-beta, TNF e and IFN-gamma [59].

Since hypertension correlated with a deeper lymphopenia and more severe disease, these effects are supposed to be mediated by higher serum angiotensin II levels, which enhance apoptosis of circulating T cells and induce a pro-inflammatory state in T cells and increased homing to the vasculature, especially in males [57,60,61]. In the elderly, the lower expression of ACE2 receptor in mouth, tongue and lower lung might paradoxically explain the high incidence of COVID-19 pneumonia. Conversely, blocking type 1 angiotensin II receptor inhibits T cell activation, [62] and reducing angiotensin II with enalapril increases circulation of T lymphocytes and polarizes macrophages toward M1-like [63]. The correlation between high levels of plasma angiotensin II documented in COVID-19 patients and viral load seems to further support this hypothesis [42]. However, it is yet unclear how during SARS-CoV-2 infection increased homing is not adequately compensated by increased bone marrow proliferation of CD8+ T cells [64]. Sex-specific differences in outcomes associated with SARS-CoV infection were independent of T and B cell responses in animal models, but rather dependent on estrogen levels [65].

Eosinopenia

Eosinopenia is a well-known hallmark of poor prognosis in patients with acute exacerbation of COPD, myocardial infarction, sepsis and stroke. As such, the score Dyspnea, Eosinopenia, Consolidation, Acidemia and Atrial Fibrillation (DECAF) can predict the in-hospital mortality of patients with acute exacerbation of COPD (AECOPD) [66]. It has been reported that 59% of COVID-19 infected individuals showed eosinopenia, [67] especially in more severe and nonresponsive cases. Interestingly, asthma or other allergic diseases were rarely reported in hospitalized patients, while drug hypersensitivity and urticaria were reported by 11.4% and 1.4%. Whereas blood eosinophil count correlates positively with lymphocyte counts of hospitalized patients, severe eosinopenia (<24/mm3) is a diagnostic marker of bloodstream infection and might therefore determine concurrent sepsis in those COVID-19 patients, who face the worst outcome [68].

Monocytopenia

Monocytopenia is common during COVID-19 infection, but a higher and rapidly increasing portion of circulating monocytes expresses an inflammatory pattern (CD14+ CD16+), especially in severe cases [67]. These monocytes showed capability of GM-CSF secretion and a high expression of IL-6, especially in severe cases, and may exert their action in the lungs after developing into macrophages or monocyte-derived dendritic cells. GM-CSF might be responsible for recruiting Th1 cells (GM-CSF+ IFN-/+) which subsequently amplify the cytokine storm inside the lung parenchyma.

Pharmacologic Options

Antiretroviral drugs proved to revert HIV-induced lymphocyte apoptosis by preserving mitochondrial transmembrane potential [69]. Similarly, direct-acting antiviral treatments for chronic hepatitis C infection, which is associated with increased immune checkpoint expressions, were reported to decrease TIM-3 and PD-L1 expression and increase T lymphocyte counts in blood in patients with sustained virological response [70]. However, no study has reported the direct cause-effect proof that immune restoration is indeed essential for curing the viral disease or can be considered a hallmark of viral control. Currently, the most commonly used drugs are chloroquine and hydroxychloroquine. Both have the potential to interfere with glycosylation of cellular receptors of SARS-CoV and inhibit both pH-dependent steps of SARS-CoV replication and autophagy, the latter being implicated in viral replication and infection [71-73]. Hydroxychloroquine has also immunomodulatory effects: it suppresses the release and production of TNF-alpha and IL-6 and inhibits autophagy. The encouraging preliminary results, in terms of reduction of symptom duration and severity of respiratory distress, led to the widespread prescription of hydroxychloroquine, which is safer than chloroquine, for prevention and treatment of COVID-19 pneumonia [74]. However, the osteoblast niche is an interesting, yet unexplored pathway. In mouse models, parathyroid hormone administration allowed to restore osteoblast number and recover from lymphopenia, in humans teriparatide increased mostly CD8+ and Treg lymphocytes [75].

A second pathway to restore a regulated immune response involves checkpoint inhibitors; in vivo data support the capability of nivolumab to expand PD-1+ T cells and restore the expression of costimulatory genes in CD8+ T cells during EBV-related hemophagocytic syndrome [76]. In animal models, anti-PD-1 and anti-PD-L1 antibodies inhibited B and T-cell apoptosis and prevented infection-induced lymphocyte depletion and death both in sepsis and in bovine diarrhea models [76]. Novel checkpoint inhibitors are going to be tested for COVID-19 patients: CD24Fc targets CD24, an innate checkpoint against the inflammatory response to tissue injury or danger-associated molecular patterns (DAMPs). CD24Fc comprises the Fc region of human IgG1 and the nonpolymorphic regions of CD24, it suppresses multiple inflammatory cytokines in healthy individuals and is effective for severe graft versus host disease (GVHD). Preclinical data reported that CD24Fc ameliorates production of inflammatory cytokines and reverses the loss and exhaustion of T lymphocytes during HIV infection [77]. The NCT04317040 randomized trial will enroll 230 patients and is currently being reviewed by the Chinese Center for Drug Evaluation.

While lymphocyte apoptosis should be prevented in patients with SARS-CoV-2 infection, on the contrary, neutrophil apoptosis might be beneficial in preventing lung damage. Both demethylating agents and phosphatidil inositol 3 kinase (PI3K) inhibitors have been proposed for inducing neutrophil apoptosis in COVID-19 patients, but only one trial is currently enrolling in this setting.

Chemokines

The inflammasome is one of the first responders during viral infection: it is a cytosolic protein complex that mediates the processing and secretion of mostly pro-inflammatory cytokines (IL-1, IL-2, IL4, IL-6, IL-10, IL-12, IL-13, IL-17, GCSF, MCSF, IP-10, MCP-1, MIP-1α, HGF, IFN-γ y TNF-α). Production of pro-inflammatory cytokine is mainly mediated by NF-kB activation, which is associated with two pathways converging onto p65 phosphorylation: IKK-2 and JAK2, the latter being the dominant way [78]. Inflammatory cytokines, in turn, regulate both innate and adaptive immune response. Inflammasome is necessary for limiting viral replication and surviving viral infections, while IL-1 did not prove to be crucial for survival in animal models of murine coronavirus infection [79].

Cytokine storms are excessive immune-mediated inflammatory response flaring out of control. They are associated with a wide variety of infections and noninfectious disease including graft-versus-host disease, autoimmune diseases, severe virus infection, multiple organ dysfunction syndromes and chimeric antigen receptor (CAR)-T cell therapy. Inflammation associated with cytokine storms may begin at one site but it spreads throughout the body via the systemic circulation.

In severe cases, higher levels of C-reactive protein, procalcitonin, ferritin and D-dimer as well as lower concentrations of albumin and hemoglobin might be explained by the higher pro-inflammatory cytokine levels and fibrinolysis in such individuals [4]. SARS-CoV infection dysregulates chemokine responses and high viral titers cause an inflammatory cytokine storm. SARS-CoV-2 has been reported to increase several factors: plasma concentration of interleukins IL-2, IL-7 and IL-10, granulocyte stimulating factor (G-CSF), interferon-gamma-inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and tumor necrosis factor alpha (TNF-Alpha) especially in moribund patients [52]. IL-6 was significantly higher (11.0 vs 6.3 pg/ml) in non-survivors versus survivor COVID-19 patients [4]. The strong correlation between IL-6 and

outcome can be explained by the thrombo-inflammatory effect of T-cell dependent signaling, predisposing platelets to an interaction with collagen receptors [80]. Data from serum and lower respiratory tract of patients infected with MERS-Cov reported higher levels of IL-1, [53] while increased IL-6 levels (54 versus 4 pg/ml) and CXCL-10 (2,642 vs 382 pg/ml) were observed only in severe cases, specifically during the second week of illness.81 In the lower respiratory tract, upregulation of the neutrophil chemoattractant chemokine IL-8, CXCR3, SOCS5 and CCR2 was also reported [81].

In the long-term regular physical exercise significantly influences muscle cell production of IL-10 (increased), TNF-alpha (decreased), IL-6 (decreased) and leptin (decreased). The above cytokine milieu diminishes the output of inflammatory leukocytes from the bone marrow while augmenting emergency hematopoiesis. Nevertheless, no study has ever attempted to quantify the protective effect of regular physical activity onto COVID-19 severity [82].

Besides cytokines, also chemokines are expected to be relevant in the pathogenesis of organ damage induced by SARS-CoV-2. Chemokine receptor 4 (CXCR4) is a multifunctional G protein-coupled receptor that is activated by its natural ligand, C-X-C motif chemokine 12 (CXCL12). CXCR4 expression is induced by hypoxia and is involved in pro-inflammatory cytokine production; it also exerts a chemo-attractive activity for various inflammatory cells, including regulatory T cells (Treg). CXCR4 and CXCL12 are also involved in regulating the recirculation and retention of both myeloid and lymphoid cells in the bone marrow. In a model of polymicrobial sepsis of previously healthy mice, blockade of CXCR4 chemokine receptor resulted in decreased CD4+ cell exhaustion and improved survival in non-neoplastic individuals [83,84]. In humans, the use of plerixafor was found to significantly affect the graft composition as there was a significantly higher proportion of the more primitive CD34+ cells, higher number of T and B lymphocytes as well as NK cells [85].

Finally, also some non-trivial pathways deserve to be reported, such as those involving calreticulin, a soluble calcium-binding protein mainly localized in the endoplasmic reticulum where it exerts several cellular function including calcium homeostasis, oxidative stress response, lectin binging, cell adhesion, cell-cell interactions, migration, phagocytosis, immune responses, cellular proliferation, differentiation and apoptosis. Calreticulin is over-expressed in animal models of ARDS and hypoxia. Its expression correlates with disease severity, while its neutralization suppresses the expression of TNF-alpha and IL-6 in macrophages by polarizing them to the M2 phenotype [85]. However, no target therapy against calreticulin is currently being tested for human use.

Anti-Chemokine and Pro-Chemokine Treatments

Corticosteroids have been firstly attempted for decreasing pneumonia-associated inflammation, since they are usually used in ARDS; dexamethasone has been shown to reduce TNF-alpha, IL-6 and VEGF in serum and bronchoalveolar lavage fluid of ARDS animal models [86], but their effect on COVID-19 patients was particularly dismal in lymphopenic patients [87]. Therefore, recommendations on the use of steroids in the different phases of COVID-19 disease are constantly updated and as no definite guidelines are available, other pharmacologic pathways might be usefully explored.

Dismal outcomes despite steroid use prompted clinicians to test monoclonal antibodies specifically targeting IL-6 receptor, namely tocilizumab and sarilumab, in order to modulate the cytokine storm. Tocilizumab can specifically bind both membrane bound IL-6 receptor and soluble IL-6 receptor and inhibit signal transduction. While the drug is approved for rheumatoid arthritis, it has been successfully used for effectively treating thrombocytopenia-anasarca-fibrosis-renal failure-organomegaly (TAFRO) syndrome [88] and pre-engraftment syndrome, [89] as well as for prophylaxis and treatment of cytokine-release syndrome in patients receiving CAR-T cells [90]. Several trials have been registered for its use in COVID-19 patients with preliminary positive results, such as rapid temperature control and respiratory functional improvement. However, the drug is actually recommended for treating patients with severe or critical disease only in clinical trials [91].

Sarilumab is a fully-human monoclonal antibody binding and blocking the IL-6 receptor and is currently being tested in US medical centers, as addition to usual supportive care, for patients with COVID-19 and respiratory failure. While the CORIMUNO-SARI trial is targeting principally sarilumab (NCT04324073), a Danish study is currently randomizing patients to different sequential treatments including tocilizumab and sarilumab (NCT04322773). Siltuximab is a monoclonal antibody targeting IL-6 directly and marketed for the treatment of HHV8-negative Castleman's disease and rheumatologic disorders. Ongoing clinical trials have preliminary shown that its activity is similar to the response of tocilizumab onto SARS-CoV-2 related inflammatory symptoms.

Inflammation associated with SARS-CoV-2 infection has been recently reported to be mediated by IL-1 release by mast cells located in the submucosa of the respiratory tract [92] and that monoclonal antibodies directed against such cytokine are expected to be useful during the hyper-cytokine

phase of the disease [93,94]. The synergic action of anti-IL6 and anti-IL1 monoclonal antibodies is currently being tested (NCT04330638). However, at the moment no trial is testing mast cell stabilizing drugs, such as ketotifen or cromolyn, or drugs directed against mast-cell mediators, i.e.histamines, anti-leukotriens or protease antagonists.

Finally, in patients with COVID-19 undergoing hemodialysis, Cytosorb [95] and other cytokine permeable membranes are currently being employed, while plasmapheresis has not being tested yet. Despite over-production of IL-1 and IL-6 may be dangerous, it was demonstrated that recombinant IL-7 (CYT107) safely improves T cell count in 390 oncologic and lymphocytopenic patients; it is currently being tested in the IRIS-7 randomized placebo-controlled trial enrolling patients with septic shock and severe lymphopenia. Preliminary results showed a 3-4 fold increase of lymphocyte count and T-cell activation without worsening of inflammation [96].

GM-CSF has also been hypothesized to play a key role in modulating innate immune response to COVID-19: serum levels have been reported to be increased during the disease and anti-CM-CSF monoclonal antibodies efficiently controller CAR-T induced cytokine storm [97]. Therefore, both namilumab (IZN-101) and lenzilumab, anti-GM-CSF monoclonal antibodies, are currently being explored in ICU patients with COVID-19. Conversely, in Belgium also sargamostin (GM-CSF) nebulized inhalation is being tested (NCT04326920) to boost innate immunity, possibly targeting the first phase of the disease.

Itacitinib is a potent and highly selective oral inhibitor of Janus kinase (JAK)-1, capable of reducing IL-6, IL-12 and interferon production in animal models of cytokine-release syndrome. It is currently being administered (200 mg daily dose) to patients receiving axi-cel or liso-cel for prevention of CD19 CAR-T cytokine release syndrome. Future testing in COVID-19 is awaited. Ruxolitinib is a JAK1/2 inhibitor which is currently being tested in a Mexican phase II trial for early COVID-19 respiratory failure due to its anti-inflammatory action, including modulation of NFkB and IL6, and its capability to decrease cytotoxic T lymphocytes and increase Treg cells (NCT04334044) [98]. Novartis is also pursuing a managed-care program with ruxolitinib 5 mg for patients with respiratory failure caused by (or possibly caused by) COVID-19 (NCT04337359). However, MERS-CoV accessory protein 4b has been proved to prevent NF-kB response possibly by competing for nuclear translocation proteins, and therefore JAK2 inhibition does not seem to have adequate anti-inflammatory results in SARS-Cov-2 infected individuals [99].

Discussion

Several pathways have been identified as main drivers in the pathogenesis of SARS-CoV-2: specific cytokines have been reported to be hallmarks of disease severity, but it is not clear which of them is the most suitable target to prevent organ damage. Lymphopenia itself, together with endothelial permeability, are relevant diagnostic and prognostic marker of the disease, but their exact role is still to be discovered. Several other pathways, such as autophagy, are yet poorly explored, or are orphan of targeted drugs, such as HIF-1alpha and HIF-2alpha.

Chloroquine, hydroxychloroquine [72-74] and several marketed drugs have been proved to reduce SARS-CoV replication in vitro, including antivirals, autophagy inhibitors (i.e. niclosamide), heparin, kinase inhibitors, proteasome inhibitors. Moreover, host-directed therapies [100] such as eculizumab, mTOR inhibitors, class III PI3K inhibitors and lysomorphic agents are being proposed for modulating disease severity [101,102]. As of 7th April 2020, more than 200 clinical trials have been registered for the treatment of COVID-19 with marketed drugs (clinicaltrials.gov), however, no umbrella trial has been designed, due to the urgent need of helping thousands of affected patients [103]. Furthermore, evidence-based medicine faces many hurdles in this emergency context: no standard comparator is suitable, intermediate clinical endpoints are undefined, several organs besides lungs are seriously involved by COVID-19, such as heart and kidneys, and iatrogenic yields of drug combination are still unknown [104].

Several drugs currently marketed for blood diseases, such as imatinib, ruxolitinib, tocilizumab and eculizumab, are currently being tested for patients with COVID-19 symptoms. Hematologists, who are expert on such drugs, are therefore called into multidisciplinary teams for managing patient selection and therapy monitoring. While awaiting vaccines and effective antiviral therapies, their expertise needs to be combined with the updated evidence on the pathogenesis of COVID-19, as they have the chance to contribute to amelioration of patient outcomes.

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