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Immune reactivity during COVID-19: Implications for treatment

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ARTICLE INFO

Keywords:

COVID-19
laboratory indexes
immune response
drug therapy

ABSTRACT

Clinical symptoms of COVID-19 include fever, cough, and fatigue which may progress to acute respiratory distress syndrome (ARDS). The main hematological laboratory findings associated with the severe form of disease are represented by lymphopenia and eosinopenia which mostly occur in the elderly population characterized by cardiovascular comorbidities and immunosenescence. Besides, increased levels of D-dimer, procalcitonin, and C reactive protein (CRP) seem to be powerful prognostic biomarkers helping to predict the onset of coagulopathy. The host immune response to SARS-CoV-2 can lead to an aberrant inflammatory response or "cytokine storm" which contributes to the severity of illness. At immunological level, patients affected by a severe form of COVID-19 show poor clinical trajectories characterized by differential "immunotypes" for which T cell response seems to play a critical role in understanding pathogenic mechanisms of disease. Also, patients with mild to severe COVID-19 displayed macrophage activation syndrome (MAS), very low human leukocyte antigen D related (HLA-DR) expression with a parallel reduction of CD4⁺ lymphocytes, CD19 lymphocytes, and natural killer (NK) cells. Corticosteroids resulted the best therapy for the immune dysregulation whereas repurposing of tocilizumab (IL-6 receptor antagonist) appears to have mixed results in patients with COVID-19. Besides, anti-coagulative therapy was associated with reduced in-hospital mortality and need of intubation among COVID-19 patients. Furthermore, the beneficial use of intravenous immunoglobulin (IVIG) and passive immunotherapy with convalescent plasma needs to be validated in large controlled clinical trials. In this review, we summarize the main hematological parameters with a prognostic value in COVID-19 and the basis of immunological reactivity during COVID-19, with a focus on ongoing clinical trials evaluating immune targets as possible therapeutic strategies.

1. INTRODUCTION

The betacoronavirus 2 (SARS-CoV-2) induces the coronavirus disease 2019 (COVID-19) [1]. This pneumonia outbreak induced a rapid pandemic [2]. A predominant mechanism of cell entry exploited by SARS-CoV-2 is represented by the binding of its spike protein to the angiotensin-converting enzyme 2 (ACE2) receptors, mostly present on pulmonary epithelial cells but also on endothelial cells, lymphocytes and other cell types. [3]. COVID-19 shows a highly heterogeneous clinical presentation ranging from asymptomatic or mild disease (more than

80% of all cases) to respiratory failure requiring mechanical ventilation and multiple organ dysfunction syndromes or failure (MODS) [4,5]. The severe form of COVID-19 occurs especially in the elderly population (65 years and older) probably owing to the higher rate of pre-existing cardiovascular comorbidities as well as increased frailty and immunosenescence [6,7]. Remarkably, dysregulated innate and adaptive immune responses triggered by SARS-CoV-2 infection, such as hyperinflammation (cytokine storm), viral escape from innate sensing (particularly the interferon I pathway, IFN-I), hyperactivation of myeloid cells, and lymphopenia characterized by T cell and NK cell

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<https://doi.org/10.1016/j.imlet.2021.01.001>

Received 14 December 2020; Accepted 3 January 2021

Available online 6 January 2021

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dysfunction seem to trigger precise immunological pathways which may contribute to COVID-19-induced systemic damages contributing to disease severity and death [8]. Besides, COVID-19 shows a significant impact on the hemostatic balance, and a pro-coagulant status may aid clinicians to identify patients with poor prognosis at an early stage of disease [9]. Therefore, the host immune response plays a key role in COVID-19 pathogenesis and seems to be different from other coronavirus infections owing to specific epigenetic-sensitive mechanisms unveiled in severe patients upon interactions between SARS-CoV-2 and host cells [10]. Now, COVID-19 is being clearly considered a hematologic disease [11], but the exact mechanistic role of both innate and adaptive immunity against SARS-CoV-2 still needs to be clarified to help to find new targets. Here, we discuss the main hematological parameters and mechanisms underlying the immunological reactivity during COVID-19 with a focus on current therapeutic strategies based on immune targets.

2. HEMATOLOGICAL RESPONSE DURING COVID-19

2.1. Laboratory findings and prognosis

COVID-19 is prevalently a respiratory infection with a prominent impact on the hematopoietic system and hemostasis underlying several cardiovascular complications [6,7]. Now, COVID-19 poses a great challenge for hematologists which should start novel therapeutic approaches going from targeted anti-inflammatory drugs to anticoagulation [11]. The dynamic changes of lymphocyte subsets and cytokine profiles of patients affected by COVID-19 and their correlation with disease severity remain unclear. In this section, we summarize the main hematological biomarkers useful to screen, evaluate, and make a prognosis for patients affected by COVID-19 (Table 1).

Generally, the incubation period (1–14 days) as well as the early phase of disease are characterized by non-specific symptoms, including fever and cough. Besides, at hematological level these patients show a normal (or slightly reduced) count of peripheral blood leukocytes (4.5 to $11.0 \times 10^9/L$) and lymphocytes (1.3 to $4.5 \times 10^9/L$) as well as normal routine laboratory tests [12–14]. Otherwise, during advanced stages of COVID-19, patients showed an aberrant immune response represented

Table 1

Main laboratory abnormalities in patients with unfavorable progression of COVID-19

Early infection		
Parameter		Values (in adults)
Peripheral blood leukocyte count	Normal (or slightly reduced)	4.5 to $11.0 \times 10^9/L$
Lymphocyte count	Normal (or slightly reduced)	1.3 to $4.5 \times 10^9/L$
Routine laboratory tests	Normal	
Hyperinflammation phase		
Peripheral blood leukocyte count	Reduced	$<4.5 \times 10^9/L$
Lymphocyte count	Severely reduced	<1500 cells/ mm^3
Eosinophil count	Reduced	<450 – 550 cells/ mm^3
Neutrophil count	Increased	$>10,000/mm^3$
Platelet count	Reduced	$<150,000/mm^3$
Inflammatory mediators	Increased levels of pro-inflammatory mediators, such as IL-6, CRP, ferritin, and PCT	IL-6 > 40 pg/ml; CRP ≥ 10 mg/L; Serum ferritin >300 ng/mL; PCT ≥ 0.5 ng/mL
Coagulative state	Increased DD	≥ 0.5 mg/L

Abbreviations: CRP: c reactive protein; DD: d-dimer; G-CSF: granulocyte colony stimulating factor; IL: interleukin; IP10: interferon- γ inducible protein 10; LDH: lactate dehydrogenase; MCP-1: monocyte chemoattractant protein-1; PCT: procalcitonin, PT: prothrombin time; TNF: tumor necrosis factor

by a modest increase in number of circulating neutrophils ($>10,000/mm^3$) and a sustained decrease in number of T lymphocytes (<1500 cells/ mm^3), mainly CD04⁺ and CD08⁺ T cells, with respect to mild cases [12–14]. A retrospective study has demonstrated that a higher reduction in number of regulatory T cells (Tregs), CD04⁺ T cells and memory cells were features of a strong imbalance of immune system in severe cases [13].

In the early phase of infection, viral clearance mediated by type-I IFN is a key signaling to prevent further viral replication, T cell exhaustion, and cytokine storm. In most of infected patients, except in those with a severe form of disease, a robust T cell activation was observed with a dominance of CD04⁺ T responses (“broadly Th1”) over CD08⁺ [15]. Besides, recovery seems to be correlated with generation of T cell memory as suggested by the missing formation of effector and central memory T cells in severe with respect to mild form of disease [16]. Remarkably, a low number of CD04⁺ and CD08⁺ T and Tregs cells might result in exacerbated inflammatory responses leading to a hyper-inflammatory immune response (cytokine storm) and worsen damaged tissue [17,18].

Sars-CoV-2 infection was characterized by a severe lymphopenia, with a drastic reduction of both CD04⁺ and CD08⁺ T cells, in moderate and severe COVID-19 cases with respect to mild symptoms [8,13]. The cause of peripheral T cell loss in moderate to severe COVID-19 remains elusive; however, beyond the established detrimental effects of the inflammatory cytokine milieu, a direct attachment of lymphocytes to the vascular wall, known as “endothelialitis” or “endothelitis”, may be one of the causes leading to lymphopenia [7]. The cytokine storm can be exploited to monitor the COVID-19 course and at laboratory level is detectable by traditional inflammatory biomarkers, including high levels of interleukin 6 (IL-6) (IL-6 > 40 pg/ml), plasma C-reactive protein (CRP) (CRP ≥ 10 mg/L), procalcitonin (PCT) (PCT ≥ 0.5 ng/mL), and ferritin (serum ferritin >300 ng/mL) which were strongly associated with higher risk of developing ARDS [14,19–20]. In particular, increased IL-6 levels have been associated with increased risk of death [21] and a gradual increase during hospitalization has been reported in non-survivors [9]. Besides, high serum CRP, procalcitonin and ferritin levels are emerged as poor prognostic factors [9]. A complex interplay between coagulative hemostasis and inflammation can trigger a coagulopathy in COVID-19, as feature of hospitalized patients affected by a severe form of disease (about 50%) [22]. Sars-CoV-2-induced coagulation disorders seem to mimic other systemic coagulopathies which are often present in severe infections, including disseminated intravascular coagulation (DIC) or thrombotic microangiopathy. In fact, standard coagulation parameters, including elevated levels of D-Dimer (DD) (DD ≥ 0.5 mg/L), are often found in patients with poor prognosis [14]. Despite the exact pathophysiological mechanisms need to be further investigated, assessing the risk of thrombosis in COVID-19 patients is critical to improve the clinical management in terms of anticoagulation therapy [23–26].

2.2. Impact of common COVID-19 complications on immune response

Obesity is an independent risk and prognostic factor for severity of COVID-19 [27]. Indeed, by affecting insulin resistance and beta-cell function, obesity can limit the ability to evoke an appropriate metabolic response during activation of immune system. At immunological level, obesity is strongly linked to a chronic pro-inflammatory state by increasing IL-6, CRP, and adipokine levels [28]. Furthermore, obesity impacts both on tissue leukocyte expression and tissue regulatory (M2) phenotypic cells which are replaced by inflammatory macrophage subsets [28]. Thus, obesity could lead to a dysregulated immune response and increased viral shedding with relevant consequences on the clinical outcomes in COVID-19 patients. Remarkably, obesity can also enhance pro-thrombotic DIC and risk of venous thromboembolism in COVID-19 [28]. To date, treatment with low molecular weight heparin can be used to limit coagulopathy in COVID-19 patients [29]. Deep vein

thrombosis occurs in the upper limbs of patients requiring continuous positive airway pressure ventilator which often can compress the superficial or deep vessels of the upper limbs, thus favoring a thrombotic damage into microcirculation [30]. The mechanistic link between SARS-CoV-2 infection and coagulopathy is not clear; however, a direct attack to endothelial cells which express high levels of ACE2 receptor may be cause of abnormal coagulative state and sepsis [31,32]. Despite prevalence of chronic obstructive pulmonary disease (COPD) is low in COVID-19, a significant severity and mortality rate is seen in these patients [33]. Specific factors, such as dysregulated local and systemic inflammation, impaired host immunity, with the predominance of CD08⁺ and CD04⁺ cells, and structural injury may potentially contribute to such risk [34]. Besides, obese patients with COPD are at increased risk of developing severe COVID-19 owing to higher levels of ACE2 expressed in bronchial epithelial samples with respect to non obese controls [35].

3. IMMUNE REACTIVITY DURING COVID-19

Immune response of patients affected by sepsis are generally classified into three clinical groups including the “macrophage-activation syndrome” (MAS) [36], “sepsis-induced immunoparalysis” (low levels of the human leukocyte antigen D related, HLA-DR, on CD14 monocytes) [37], and an “intermediate functional state” without a clear dysregulation. Since IL-6 can inhibit HLA-DR expression [38], we could hypothesize that IL-6 over-production may be correlated with a lower HLA-DR expression in COVID-19 supporting the ongoing clinical investigations about the putative efficacy of anti-inflammatory drugs [39,40]. Moreover, the NK group 2 member A (NKG2A) receptor which can inhibit both NK cytokine secretion and cytotoxicity resulted overexpressed on both CD08⁺ T and NK cells of patients affected by COVID-19 vs healthy controls [41]. Since NKG2A overexpression can also lead to CD08⁺ T cells and NK exhaustion (a state of functional unresponsiveness) [41], SARS-CoV-2 may use this strategy to manipulate the host immune response against the viral pathogen. Monalizumab is an inhibiting antibody against NKG2A which can restore the function of CD08⁺ T and NK cells in cancers, thus may be a putative useful drug to treat patients affected by COVID-19 [41]. The B cell response is critical for the virus clearance and is the major responsible for the memory response preventing reinfection. SARS-CoV-2 can trigger a robust B cell response, as demonstrated by the rapid virus-specific IgM, IgG and IgA, and neutralizing IgG antibodies in the days following infection [8]. In most patients affected by COVID-19, the seroconversion occurs between 7 and 14 days after the onset of symptoms, and antibody titers may persist for a long period after clearance of the virus (36-50 days) but it is not clear whether and how antibody responses may contribute to disease [8]. From evidence, the cumulative IgM and IgG seroprevalence was 44% and 56%, respectively, on day 7 after the onset of symptoms and reached over 95% on day 20 and day 16, respectively. Besides, IgM and IgG levels appeared to remain above the cutoff value on day 28 [42]; and the long-term coexistence of IgG with SARS-CoV-2 raises the question of whether patients with antibodies are still at risk for re-infection [43]. Thus, one of the major challenges is to understand the mechanistic bases by which SARS-CoV-2 can overcome the presence of specific IgG antibodies for such a long time [44].

Innate immunity seems to play a pivotal role in SARS-CoV-2 clearance [45]. One strategy to pursue is to use drugs that mimic viral RNA in order to contribute to clearance of SARS-CoV-2. For example, combination of vaccine and innate immune stimulators may be more effective in the rapid clearance of SARS-CoV-2 [46]. Importantly, FDA has recently approved two mRNA-based vaccines (Pfizer/BioNTech and MODERNA) for their distribution in U.S. which demonstrated to prevent severe COVID-19. These vaccines are based on mRNA technology which, instead of inoculating the antigen towards which an immune response is to be induced, inoculates the genetic sequence with instructions for producing the antigen (Spike protein)(<https://www.who.int/>). Both the

increased proinflammatory responses and the reduction of antiviral cytokines in elderly people (the so called immunosenescence) may explain why disease severity and fatality are higher in aged COVID-19 patients [6,7]. In fact, the effective CD08⁺ T cell response might influence the severity of disease whereas variation in IL-10 levels might contribute to the relatively mild pneumonia symptoms in children affected by COVID-19 [31,32]. All patients affected by severe forms of COVID-19 display exaggerated inflammatory responses (immune dysregulation or MAS) which are characterized by pro-inflammatory cytokines. In particular, IL-6 can drive the immune dysregulation whereas IL-1 β can guide MAS. At hematological level, immune dysregulation is featured by a monocyte-related cytokine overexpression and lymphopenia, mainly regarding CD04⁺ T and subsequently B cell count, CD08⁺ T and natural killer (NK) cell reduction leading to a higher risk of developing secondary bacterial infection [31,32]. Thus, the adaptive immune response might not be successfully triggered by immune system. Despite molecular mechanisms underlying lymphopenia are still unknown, it may be possible that SARS-Cov-2 can use a further strategy to directly infect circulating T cells and promote the cell death without taking advantage from ACE2 receptor which is absent in circulating lymphocytes [31,32].

SARS-CoV-2-specific memory T cells can persist in peripheral circulation providing a protective immunity [47]. Therefore, T cells studies may elucidate pathways for diagnostics of COVID-19 and to understand the cellular and molecular ways underlying the high clinical heterogeneity of disease.

4. INSIGHTS ON IMMUNE-BASED THERAPIES FOR COVID-19

During the first months of pandemic, the therapeutic arms seemed to be specific FDA-approved interleukin receptor antibodies mainly including tocilizumab and anakinra prescribed for systemic inflammatory response; however, later companies that produced tocilizumab stopped their randomized controlled studies in COVID-19 due to failure [48]. Thus, we are left with mainly some third degree observational studies to support the relevance of IL-6 in treating COVID-19 (Table 2). And, neither tocilizumab nor anakinra should be used in COVID-19 unless in an approved trial. Additional targets include IL-1 receptor [49], TNF- α [50] and interferon (IFN). On the other hand, multiple clinical trial groups around the world launched high-quality randomized clinical trials of corticosteroids for severe COVID-19 [51]. The UK-based RECOVERY trial has enrolled 6425 patients (2104 randomized to receive dexamethasone and 4321 randomized to receive usual care) and treatment with dexamethasone (6 mg/d for 10 days) was able to reduce mortality in patients receiving mechanical ventilation and supplemental oxygen as compared to usual care alone [52]. Besides, the REMAP-CAP trial randomized 403 patients with severe COVID-19 and receiving respiratory or cardiovascular organ support) to 1 of 3 open-label groups: fixed low-dose hydrocortisone, shock-dependent hydrocortisone, or no hydrocortisone. As a results, fixed-dose hydrocortisone and shock-dependent hydrocortisone were both likely superior to no hydrocortisone, but data were insufficient to confirm a single optimal regimen [53]. Moreover, controlled clinical trials are investigating the therapeutic efficacy of a humanized anti-granulocyte colony stimulating factors (GM-CSF) IgG1 monoclonal antibody TJ003234 (Table 2). Janus kinase (JAK1/JAK2) inhibition and the use of I IFN (β 1 α and β 2 α) are under consideration for severe patients affected by COVID-19. Type I IFN signals through JAK-STAT pathway and upregulated IFN-sensitive genes would eliminate infected cells. Other approaches are coming from pooled plasma of healthy donors, and intravenous immunoglobulin (IVIG) which represent one of the most widely diffused immunotherapies in many inflammatory diseases [54]. Some preliminary studies indicate that IVIG may be useful also during COVID-19 [55,56]; however, it is needed a randomized clinical trial with a large number of patients to verify the effectiveness of this therapy. Other therapeutic options would be to use convalescent plasma, intravenous hyperimmune

Table 2
Immune drugs under clinical investigation in COVID-19 disease

Mechanism of drug action	Trial	n Patients/status
IL-1 receptor antagonist <i>Anakinra</i>	Phase 3 (NCT04330638)	342 participants/Active Not Recruiting
	N/A (NCT04318366)	1000 participants/ Recruiting
	EudraCT Number: 2020-001825-29	Ongoing
	EudraCT Number: 2020-001734-36	Ongoing
IL-6 neutralization <i>Siltuximab</i>	Phase 3 (NCT04330638)	342 participants/Active Not Recruiting
	EudraCT Number: 2020-001500-41	Ongoing
	EudraCT Number: 2020-001413-20	Ongoing
IL-6 receptor antagonist <i>Sarilumab</i>	Phase 2 (NCT04315298)	400 participants/ Completed
	Phase 2 (NCT04321993)	1000 participants/ Recruiting
	Phase 2/3 (NCT04327388)	300 participants/ Completed
	EudraCT Number: 2020-001634-36	Ongoing
	EudraCT Number: 2020-001162-12	Ongoing
	Phase 2 (NCT04317092)	400 participants/Active Not Recruiting
Tocilizumab	Phase 3 (NCT04324073)	239 participants/Active not recruiting
	Phase 3 (NCT04320615)	330 participants/ Completed
	Phase 3 (NCT04330638)	342 participants/Active Not Recruiting
	EudraCT Number: 2020-001386-37	Ongoing
	EudraCT Number: 2020-001375-32	Ongoing
TNF inhibitor <i>Baricitinib</i>	EudraCT Number: 2020-001770-30	Ongoing
	Phase 2 (NCT04330638)	1000 participants/ Active Not Recruiting
	Phase 3(NCT04330638)	200 participants/Active Not Recruiting
Inhibition of viral replication by inducing type I IFN- stimulated genes <i>IFNβ1α</i>	EudraCT Number: 2020-001367-88	Ongoing
	EudraCT Number: 2020-001321-31	Ongoing
Recombinant human IFN α1β	Phase 1(NCT04330638)	328 participants/Active Not Recruiting
Recombinant human IFN α2β	Phase 3 (NCT04315948)	3100 participants/ Recruiting
Inhibition of complement activation by binding to terminal complement protein C5 <i>Eculizumab</i>	Phase 3 (NCT04320238)	2944 participants/ Recruiting
	Phase 1 (NCT04288713)	N/A/Available
Regulation of innate response to inflammatory stimuli and injury by binding to danger-associated molecular patterns and Siglec G/10 <i>CD24F</i>	EudraCT Number: 2020-001246-18	Ongoing
GM-CSF neutralization <i>Anti-GM-CSF Monoclonal AB</i>	Phase 3 (NCT04317040)	230 participants/Active Not Recruiting
GM-CSF neutralization, inhibition of viral	Phase 2 (NCT04341116)	144 participants/ Recruiting
	Phase 1/2 (NCT04341116)	90 participants/ Recruiting

Table 2 (continued)

Mechanism of drug action	Trial	n Patients/status
infection of alveolar cells and virus clearance <i>NKG2D-ACE2 CAR-NK Cells</i>		

Abbreviations: ACE2: angiotensin-converting enzyme 2; CAR: chimeric antigen receptor; GM-CSF: granulocyte-macrophage colony-stimulating factor; N/A: not applicable; NK: natural killer; NKG2D: NK group 2 member D.

globulin or neutralizing monoclonal antibodies (Table 3). Clinically, it is mandatory to validate the neutralizing activity of plasma or antibody preparations before their use in severe patients affected by COVID-19, mostly for convalescent plasma. Although there is a variable, temporal window, seroconversion time for IgM and IgG following onset of the disease was day 12 and 14, respectively, with 95% of infected patients who displayed IgM and 80% for IgG [57]. Preliminary reports suggested that plasma therapy may lead to improvement in around 35% of treated patients [58,59]. However, we still need to standardize the methodological steps necessary to make convalescent plasma treatments safe and readily available for treating COVID-19 patients [60]. In fact, patients affected by severe COVID-19 received convalescent plasma at a median of 21.5 days after first detection of viral shedding [61]. Results indicated that convalescent plasma treatment can discontinue SARS-CoV-2 shedding but cannot reduce mortality in critically end-stage patients, thus suggesting the need to start treatment earlier.

5. ANTICOAGULATIVE THERAPY IN COVID-19

Hemostatic and inflammatory modifications are common in severe manifestations of COVID-19, and both the bedridden status and critical illness may constitute a prothrombotic milieu predisposing to venous and arterial thrombosis [62]. Hypercoagulable responses may result from specific interactions between host defense mechanisms and the coagulation system [63]. Often, D-dimer and factor VIII and von Willebrand factor are elevated and accompanied by complement activation, platelet activation, increase in fibrinogen, and neutrophil extracellular traps via epigenetic mechanisms [10,64,65]. Besides, some studies have also found antiphospholipid antibodies in patients with COVID-19 and heparin resistance [66,67]. Anticoagulation is associated with reduced in-hospital mortality and need of intubation among COVID-19 patients. However, the optimal antithrombotic regimen for patients with COVID-19, especially those with severe disease, remains uncertain and is currently an area of active clinical interest. A single-city, retrospective study enrolled 4400 adults admitted to New York City hospitals with COVID-19 of which 45% received prophylactic anticoagulation, 21% received therapeutic anticoagulation, and the remainder received none [68]. Overall, 24% of the patients died in the hospital. After multivariable adjustment, prophylactic and therapeutic treatment were each associated with about a 50% reduction in mortality, relative to no anticoagulation. Besides, thromboembolic disease was found in 42% of autopsies related to patients who did not received therapeutic anticoagulation [68]. The recently launched FREEDOM COVID-19 trial (Phase 4, NCT04512079) is evaluating prophylactic and full-dose enoxaparin as well as apixaban in 3600 hospitalized COVID-19 patients. However, no study results have been posted yet. Besides, the optimal type, dose, and duration of intermediate versus prophylactic doses of anticoagulative drugs (enoxaparin, eparin, enoxaparin/lovenox) is being tested in the ongoing randomized IMPROVE trial (Phase 4, NCT04367831) [69].

6. CONCLUDING REMARKS

COVID-19 cannot be considered a disease limited to lungs or

Table 3
Immune treatments with immunoglobulin or immune plasma

Treatment	Aim	Dose	Trial	n Patients/status
IVIG	Suppression of innate and adaptive inflammatory responses	0.5g/kg/d for 5 days	Phase 3 (NCT04261426)	80 participants/Not yet recruiting
		0.5 g/Kg for 4 days	Phase 3 (NCT04350580)	138 participants/ Recruiting
		0.5g/kg/d for 3 days	Phase 4 (NCT04411667)	40 participants/ Active Not Recruiting
		Polyvalent IVIG in combination with the standard management	EudraCT Number: 2020-001768-27	39 participants/ Ongoing
		High dose IVIG plus SMT	EudraCT Number: 2020-001696-32	100 participants/ Ongoing
Immunoglobulin from cured patients	Viral inactivation	0.2g/kg, ivdrip, once a day, for 3 days	Phase 1 (NCT04411667))	10 participants/Active Not Recruiting
Human coronavirus immune plasma	Viral inactivation	1 unit; ~200-250 mL collected by pheresis	Phase 2 (NCT04323800)	150 participants/ Recruiting
Hyperimmune plasma	Viral inactivation	Administration of hyperimmune plasma at day 1 and based on clinical response on day 3 and 5	Phase 1 (NCT04321421)	49 participants/ Completed
		Administration of two units of 300 mL Plasma hyperimmune plus standard therapy	Phase 2 (NCT04392414)	60 participants/ Completed
Anti-SARS-CoV-2 inactivated convalescent plasma	Viral inactivation	N/A	Phase 2/3 (NCT04385043)	400 participants/ Recruiting
		N/A	Phase 1 (NCT04292340)	15 participants/ Recruiting
		Day 0, Day 1: Transfusion of 200mL of ABO -Rh compatible inactivated convalescent plasma	Phase 2 (NCT04385186)	60 participants/Not yet recruiting
		N/A	EudraCT Number: 2020-001310-38	Ongoing
		1-2 units of ABO matched donor plasma at neutralization antibody titer >1:64	Phase 1 (NCT04333251)	115 participants/Not yet recruiting
Convalescent plasma	Viral inactivation	N/A	Phase 1 (NCT04327349)	30 participants/ Enrolling by invitation
		Day 1: CP-COVID19, 250 milliliters. Day 2: CP-COVID19, 250 milliliters.	Phase 1/2 (NCT04366245)	72 participants/ Recruiting
		4 units of convalescent plasma	Phase 2 (NCT04429854)	10 participants/ Completed
		200 cc of convalescent plasma	Phase 2 (NCT04393727)	423 participants/ Recruiting
		Day 1: CP-COVID19, 250 milliliters. Day 2: CP-COVID19, 250 milliliters. Hydroxychloroquine: 400 milligrams each 12 hours for 10 days	Phase 2 (NCT04332835)	126 participants/ Recruiting

Abbreviations: IVIG: intravenous immunoglobulin; N/A: not applicable; SMT: standard medical treatment.

cardiovascular system, rather it is a systemic infection with a relevant impact on the hematopoietic and coagulative systems. Lymphopenia shows a higher prognostic value together with inflammatory indices, including CRP and IL-6 which are useful to diagnose the cytokine storm and then stratify patients with poor disease progression. Coagulation abnormalities, such as elevated D-Dimer, PT and fibrin degradation products are particularly associated with disease worsening. The evaluation of individual immune response is currently part of the clinical evaluation; however, there are many questions about the immunity-based protection which remains unsolved owing to the clinical heterogeneity (from asymptomatic to mild symptoms), the association between presence of delayed/weak antibody responses and severe outcomes, and the long-time coexistence between the virus and its specific IgG. Now, it is clear that SARS-CoV-2 infection can both impair and hyperactivate the immune system [70], and patients affected by a severe form of COVID-19 seem to be characterized by differential “immunotypes” associated with poor clinical trajectories [71]. A timely administration of treatments may reduce viral load and avoid hyperactivation of pro-inflammatory pathways. Two mRNA-based vaccines have been recently approved as preventive strategy in order to teach our innate immune system as fight Sars-CoV-2. Hyper-inflammation is caused by a cytokine storm which results from an exaggerated immune response to the presence of SARS-CoV-2. This is considered one of the most powerful biomarkers of poor prognosis in patients affected by COVID-19. To date, no specific treatment has been proven to be effective; however, corticosteroids resulted the best therapy for the immune

dysregulation. Many ongoing clinical trials are investigating new off-label therapeutic possibilities to reduce mortality and admission to mechanical ventilation rates, including the optimal antithrombotic regimen. Promising results were obtained by using hyperimmune plasma from patients recovered from the disease as well as repurposing of corticosteroids. More large clinical studies are required to assess the combination therapy really effective and safe in treatment of patients with moderate to severe form of COVID-19 in the second wave of pandemics [72,73].

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding to declare.

Author's contribution statement

CN, GB, CC wrote the manuscript. MF, CL, and MR supervised the final version. All 6 the authors have read and approved the manuscript.

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