Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Therapie 76 (2021) 335—345

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

THERAPEUTICS

Harnessing immunotherapy to combat COVID-19: A modern snake oil or silver bullet?

Shivshankar Malkarjun Gunjegaonkar[a], **Thukani Sathanantham Shanmugarajan**[b,*], **Mohanasundaram Arunsundar**[b], **Uppuluri Varuna Naga Venkata Arjun**[b], **Kadirrel Devi**[b], **Sagar Baliram Wankhede**[a], **Velayutham Ravichandiran**[c]

[a] *JSPM's Charak College of Pharmacy and Research, Pune-Nagar Road, Wagholi, Pune, 412207 Maharashtra, India*
[b] *Vels Institute of Science, Technology and Advanced Studies, School of Pharmaceutical Sciences, Department of Pharmaceutics, Pallavaram, Chennai, 600117 Tamil Nadu, India*
[c] *National Institute of Pharmaceutical Education and Research (NIPER), 700054 Kolkata, India*

Received 27 May 2020; accepted 22 October 2020
Available online 1 November 2020

KEYWORDS
COVID-19 serotherapy;
COVID-19;
Immunotherapy;
Monoclonal antibodies;
Interferon type I

Summary Coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has emerged into a global health and economic menace. Amidst the COVID-19 turmoil, recent failures/uncertain outcomes in clinical trials involving the anti-malarial (hydroxychloroquine), anti-viral (remdesivir) or the combination of anti-malarial/antibiotic (hydroxychloroquine/azithromycin) regimens have predisposed the physicians to distrust these ''highly-touted'' drugs for COVID-19. In this milieu, immunotherapy might be a credible modality to target or modify specific/non-specific immune responses that interfere with the survival of intracellular pathogens. This scientific review throws light on the epidemiology of COVID-19, its pathogenesis and the current clinical scenario of immunotherapeutics including convalescent plasma (CP), type-1 interferons (IFN—I) and human monoclonal

* Corresponding author. Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Chennai, 600117 Tamil Nadu, India.
E-mail address: shanmuga5@yahoo.com (T.S. Shanmugarajan).

https://doi.org/10.1016/j.therap.2020.10.004

antibodies (mAbs) to combat COVID-19. The treatment outcomes underscore that immunotherapy might be a reliable tool to assuage COVID-19-associated immunopathology. However, specific patient pool studies are warranted to ascertain the precise (re)purposing of immunotherapeutics for COVID-19.

Abbreviations

ACE2	angiotensin converting enzyme 2
ARDs	acute respiratory distress syndrome
COVID-19	coronavirus disease 2019
CP	convalescent plasma
FGF2	fibroblast growth factor
GGOs	ground glass opacities
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
HIS	hyperinflammatory syndrome
IFN-I	type-1 interferons
IL	interleukines
IRF3/7	IFN regulatory factor 3/7
ISGs	interferon stimulated genes
ISRE	interferon simulated response elements
JAK2	Janus kinase
mAbs	human monoclonal antibodies
MDA 5	melanoma differentiation associated protein 5
MHC	major histocompatibility complex
NF-kB	nuclear factor kappa B
PAMPs	pathogen-associated molecular patterns
PRRs	pattern-recognition receptors
RBD	receptor binding domain
RIG-1	retinoic acid inducible gene 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus

Introduction

The novel coronavirus strain, termed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is notoriously known to cause the fatal coronavirus disease 2019 (COVID-19) [1]. The pathogenesis and signaling mechanisms underpinning SARS-CoV-2 infection is not fully understood and is under investigation. Despite the obscure information regarding the human immunological response to SARS-CoV-2 infection, research findings and perspectives about SARS-CoV and MERS-CoV infections throw light on the possible pathological mechanisms underlying SARS-CoV-2 infection.

Viral entry and its recognition by host cell

The association of angiotensin-converting enzyme 2 (ACE2) receptor expressed on the host cell and COVID-19 surface spike receptor-binding domain (RBD) is the initial step followed by fusion of viral particles within the cell membrane [2]. Studies strongly suggested that angiotensin-converting enzyme 2 (ACE2) receptor expressed on the lung epithelial cells is the key entry port for viral invasion [2,3]. Structural re-organization of the viral surface S-protein facilitates the fusion between viral membrane and the host cell membrane, resulting in the release and replication of SARS-CoV-2 genomic RNA within the host cell. The viral genome or the viral replication intermediates are the pathogen-associated molecular patterns (PAMPs) sensed by the innate immune system through an array of pattern-recognition receptors (PRRs) including toll-like receptors (e.g., TLR3 and TLR7), cytosolic/endosomal RNA sensors, retinoic-acid inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) [4,5].

The ''cytokine burst'' response

The PAMP-PPR interaction leads to the activation of downstream nuclear factor-kappa B (NF-κB) and IFN regulatory factor 3/7 (IRF3/7) signaling pathway through their translocation into host cell nucleus. NF-κB triggers the activation of proinflammatory cytokines, such as TNF-α and interleukins (IL-1β and IL-6), leading to IFN-γ and IL-17 secretion. Further, via, a heterodimeric receptor complex of interferon alpha receptors (IFNAR1/IFNAR2), type I IFNs (IFN-α and IFN-β) are activated by IRF3/7. IFNγ, is an important lymphokine is involved in the activation of the antigen-presenting cells (APC), including dendritic cells and macrophages and induction of class II major histocompatibility complex (MHC) molecule expression. IL-17 promotes the secretion and activation of granulocyte colony-stimulating factors (G-CSF), while IL-17 along with granulocyte-macrophage colony-stimulating factor (GM-CSF) triggers inflammation through Janus kinase 2 (JAK2) signaling [6]. Current clinical investigations showed significantly increased in blood levels with cytokines including TNF-α, interleukins (IL1-β, IL7, IL8, IL9, IL10), IFNγ, fibroblast growth factor (FGF2), G-CSF and GM-CSF. Some of the cases with severity showed enhanced levels of (IL-2, 7, 10) [1,7]. In a cascade of event-specific signaling, type I IFN via IFNAR activates the JAK-STAT1/2 (STAT; signal transducer and activator of transcription proteins) pathway and causes phosphorylation of STAT1 and STAT2 through kinases (JAK1 and TYK2) [8]. Further phosphorylated STAT1/2 associated and forms a complex with

IRF9 and translocates to host nuclei. This complex initiate interferon-stimulated genes (ISGs) under the influence of interferon stimulated response elements (ISRE) and suppresses viral replication and further infection in early stage [7,9]. It is proposed that coronavirus infection enhances influx of neutrophils and monocytes-macrophages which lead to increased immunological responses in lung epithelial and causes respiratory congestion and showed delayed asymptomatic responses in individuals [10,11]. It was also observed that the prevalence in children and young adults were less due to prominent efficient inbuilt immunity. These data strappingly indicate that innate immune response is a critical factor for disease effect. On extensive literature review, it is proposed that innate immunity plays a crucial role and inhibiting important cytokines, enhancing IFN and boosting immunity will be effective strategies in controlling the COVID-19 infection and its propagations [12,13].

Current scenario of COVID-19 therapies

Hitherto, there is no FDA-approved disease modifying drug to treat COVID-19. Recent failures/uncertain outcomes in clinical trials involving the ''highly touted'' anti-malarial (hydroxychloroquine), anti-malarial plus antibiotic combination (hydroxychloroquine plus azithromycin) and anti-viral (remdesivir) drugs are creating distrust in the use of these drugs for COVID-19 [14—16]. These reports accentuate that there is a dire need for deployment of newer strategies like immunotherapy to combat COVID-19.

Immunotherapy for COVID-19

Convalescent plasma

Activation of humoral immunity is possible with administration of convalescent plasma (CP), collected from humans who have suffered from COVID-19 and got cured [17]. CP contains SARS-CoV-2 specific antibodies and able to provide short term immunization against infectious disease [17]. The circulating pathogens are rapidly neutralized and eradicated by administration of CP in initial course of infection [18,19]. Recent 5 clinical investigation in human beings with administration of CP showed promising treatment option as CP reduced mortality rate in severe and clinically ill patients, eradication of SARS-CoV-2 RNA by increasing neutralizing antibody titers and improvement in clinical symptoms [20]. Shen C et. al. (2020) showed that CP has improved the clinical outcome in the five critically ill patients with uncontrolled COVID-19 and acute respiratory distress syndrome (ARDS) [21] (Table 1). Following CP transfusion, an appreciable reduction in viral load, increased neutralizing antibodies and improvement in ARDS were observed. Three-out-of-five patients were discharged after 52—55 days and two were stable after 37 days of CP administration. Another clinical finding of 10 critical adult patients showed improvement in clinical symptoms and laboratory parameters, increased in neutralizing antibody, increase of oxyhemoglobin saturation and lymphocytes, decreased C-reactive protein and lung lesions in radiological examination [22]. Rojas et al. (2020) proposed that the ameliorative effect of CP against COVID-19 involves direct viral neutralization, regulation of immune-hyperactivity (in terms of cytokine burst, Th1/Th17 ratio, activation of complement system) and control of hyper coagulopathy [23]. A recent clinical investigation carried by Ye M et al. at Wuhan, China comprised the treatment of six clinically ill (50—70 years) COVID-19 positive patients with ABO-compatible convalescent plasma. The clinical and radiological features after treatment of ABO-compatible convalescent plasma showed significant improvement in clinical symptoms. Serum analysis confirmed a remarkable surge in anti-SARS-CoV-2 IgM and IgG. CT scan of the chest showed resolved focal pulmonary GGO's (ground-glass opacities) in all the 6 patients. Furthermore, the study advocated no significant adverse effects upon ABO-compatible convalescent plasma treatment [24]. In a phase 2 clinical trial in 86 severally ill adult patients, carried out at Columbia University medical center, USA, significant improvement in clinical symptoms in severely ill patients. The clinical outcomes were assessed based on the duration from randomization to either discharge from the hospital or improvement by one point on the following seven-point ordinal scale, whichever occurs first [25].

Clinical investigation of convalescent plasma therapy in two COVID-19 positive patients with acute respiratory distress syndrome was carried out in Yonsei University College of Medicine, Seoul, Korea. The study displayed a striking increase in anti-SARS-CoV-2 IgG antibody, normalized body temperature, subsided oxygen demand, decreased CRP and IL-6. Clinical symptoms were abolished and PaO2/FiO2 was increased to 300, radiological examination indicated resolution of both lung infiltrates. Both patients became COVID-19 negative and survived without showing any significant adverse effect of convalescent plasma therapy [26]. Houston Methodist hospitals investigated the therapeutic benefit of convalescent plasma therapy in 25 severally ill patients. Clinical outcome and improvement in COVID-19 symptoms were assessed according to the modified WHO 6-point ordinal scale and laboratory parameters [27]. Hospital of Zhejiang University, China carried out a clinical investigation using convalescent plasma treatment in 19 patients (11 males and 8 females). Among them, 10 was severely ill and 9 were critically ill. The result indicated a progressive and marked improvement in clinical outcomes. Patients treated with convalescent plasma showed improved lymphocytopenia, an index of immunomodulation, as well as improved C-reactive protein and SaO2 indicating recovery from lung damage [28]. The first 2 cases tested COVID-19 positive were treated with convalescent plasma and investigated for clinical improvement at the National Institute of Hematology and Infectious Diseases, Hungary. Results indicated that convalescent plasma treatment improved oxygenation, decreased inflammatory markers, increased lymphocyte counts, and decreased IL-6 levels. Mechanical ventilator was removed from both patients after 2 weeks of treatment [29] (Table 1).

Interferon-based therapy

Families of natural proteins secreted by immune system cells (WBC's, NK cells, epithelial cells etc.) like interferons are another approach in the treatment of infectious diseases [30]. Several classes of interferons have been identified for clinical utility amongst them interferon-beta 1a is under

Table 1 Immunotherapy-based clinical trials and outcomes in COVID-19 patients.

Immunotherapy	Name of bioactive agent and country	Combination Therapy	Patient type and number	Clinical outcome	Percent recovery	References
CP	Convalescent plasma infusion (China)	Mechanical ventilation, antiviral and prednisolone	5 critically ill patients	Decreased IL-6 and CRP, resolution of pulmonary lesions, normalised body temperature, viral loads also decreased	60 (2 patients were not yet discharging)	Shen C et al., 2020 20
	Convalescent plasma infusion (China)	Arbidol monotherapy or combination therapy with remdesivir/antibiotics/methylprednisolone	10 critically and clinically ill	Increased oxyhemoglobin saturation, relief from dyspnea, decreased C-reactive protein, improved lung lesion and viremia, improved laboratory parameters	100	Duan K et al., 2020 21
	ABO-compatible convalescent plasma (China)	Arbidol and oxygen treatment	6 clinically ill aged patients	Ani-SARS-CoV-2 IgM and IgG. Resolved focal pulmonary GGO's	100	Ye at al., 2020 23
	Convalescent plasma (Korea)	Intubation, mechanical ventilator corticosteroid, lopinavir/ritonavir, hydroxychloroquine and empirical antibiotics	2 clinical ill (man-71, women-67)	Increased anti-SARS-CoV-2 IgG antibody, no fever, decreased CRP, IL-6, oxygen demand, lung infiltrates PaO2/FiO2	100	Ahn et al., 2020 25
	Convalescent plasma (China)	—	19 patients (11 males and 8 females; 10 severely ill and 9 critically ill)	Improved lymphocytopenia, immunomodulation; C-reactive protein and SaO_2	100	Chen et al., 2020 27
	Convalescent plasma (Hungary)	—	2	Improved oxygenization, lymphocyte counts decreased inflammatory markers, decreased IL-6, level	100	Bobek et al., 2020 28
	Convalescent plasma (Turkey)	Favipiravir, isoniazid, rifampin, pyrazinamide, ethambutol, oxygen supplementation, tocilizumab	1 (54-year-old male patient with systemic tuberculosis and kidney disease	Improved oxygen saturation, decrease in inflammatory markers and IL-6, resolved GGO's	100	Çınar et al., 2020 [30]

Table 1 (*Continued*)

Immunotherapy	Name of bioactive agent and country	Combination Therapy	Patient type and number	Clinical outcome	Percent recovery	References
INF	INF (China)	Antiviral, Kaletra, antibacterial and corticosteroids, mechanical ventilation, oxygen supply	135 clinically and critically ill	Improved oxygen saturation, lymphocyte, CD4+ T, CD8+ T, B cell, and NK, resolved GGO's	99.30	Wan et al., 2020 34
	INF beta-1b (Hong Kong)	Lopinavir-ritonavir, and ribavirin	127 (86 treated and 41 control)	Decrease in viral load, cytokine response, resolved GGO's and shortening duration of hospitalization	100	Hung et al., 2020 35
	INF (China)	Remdesivir, lopinavir-ritonavir, and corticosteroids.	237 (158 treated and 79 placebo)	Improvement in clinical symptoms, oxygen saturation, reduced respiration rate, fever, suppressed cough	100	Wang et al., 2020 36
	INF-Alpha (China)	Lopinavir—ritonavir	36 children	Improved clinical symptoms, oxygen saturation, immune cell count, resolved GGO's.	100	Qiu et al., 2020 37
	INF-beta (Iran)	Dexamethasone and immunoglobulin	105 critically ill	Improvement clinical symptoms, SpO2 level, shorten hospitalisation of patients, no mechanical ventilation.	ongoing	Abdolahi et al., 2020 38
	Type 1 INF (Turkey)	Hydroxychloroquine, azithromycin and enoxaparin sodium	1 clinically ill (multiple sclerosis)	No symptoms, normal respiration, WBC, Hb, platelet count, CRP level, liver and kidney function tests, D-Dimer levels.	100	Gemcioglu et al., 2020 39
	INF beta-1a (Iran)	Hydroxychloroquine, and lopinavir/ritonavir	20	Subsides symptoms resolved GGO's, reduced ICU stay and mortality rate	-	Dastan et al., 2020 [41]
	IFN-α2b (China)	Combination of arbidol, prophylactic antibiotic regimens, oxygen supplementation	77 hospitalized patients	No signs or symptoms of end organ dysfunction, respiratory distress, improved oxygen saturation, decreased in viral load and IL-6, CRP levels	100	Zhou Q et al., 2020 [42]
Human mAbs	Tocilizumab (Iceland)	Intravenous ceftriaxone and oral azithromycin 5 days of oral hydroxychloroquine, respiratory intubation	1 patient with history of asthma and hypertension	Improved oxygen saturation from 88% to 95%, reduced TNFα and IL-6, reduced fever, cough, weakness	100%	Bjornsson et al., 2020 [47]

Table 1 (*Continued*)

Immunotherapy	Name of bioactive agent and country	Combination Therapy	Patient type and number	Clinical outcome	Percent recovery	References
	Tocilizumab (China)	Antiviral therapy of lopinavir/ritonavir, IFN-α routine therapy	20 patients (4 Critically ill)	Temperature returned to normal, improved oxygen saturation, significant change in CRP, percentage lymphocytes, IL-6 and lung lesions, reduction in viral load	100%	Xu X et al., 2020 [50]
	Leronlimab (USA)	—	10 terminally-ill, critical	Reduction in plasma IL-6, viremia, restores CD4/CD8 ratio, improved clinical outcomes	100%	Patterson BK et al., 2020 [52]
	Mavrilimumab	—	6 patients	Improved oxygenation and reduced fever	100%	Nold C. et al., 2020 [54]
	Siltuximab (USA)		21 (9 critically ill)	Significant change in IL-6 and CRP	95%	Gritti G 2020 [57]
	Tocilizumab (China)	Moxifloxacin, Arbidol, methylprednisolone	1 (clinically ill patient with multiple myeloma)	Improved oxygen level, breathing, absence of chest tightness, decreased IL-6 level, normal lymphocyte count and resolved GGO's.	100	Zhang et al., 2020 [57]
	Tocilizumab (Italy)	—	100 clinically ill (hyperinflammatory syndrom)	Improved acute respiratory failure, resolved diffuse bilateral opacities, and abolished symptoms	76	Toniati et al., 2020 [58]
	Tocilizumab (France)	Hydroxychloroquine	1 (with sickle cell syndrome)	Improvement in general condition, radiological examination and observed SpO2 at 97%	100	De Luna et al., 2020 [59]
	Tocilizumab (Italy)	Hydroxychloroquine	1 (kidney transplant recipient)	No fever was absent, improved oxygen saturation, reduced respiration rate and normalised WBC count	100	Fontana et al., 2020 [60]
	Tocilizumab (China)	Methylprednisolone	15 (2 moderately ill, 6 seriously ill and 6 critically ill)	Decreased CRP, improved/stabilise symptoms, reduced inflammatory activity and IL-6 levels	66	Luo et al., 2020 [19]
	Tocilizumab (Italy)	Lopinavir/ritonavir hydroxycholoroquine	3 (clinically ill)	Absence of fever, improved clinical symptoms and oxygen saturation, reduction in CRP levels	100	Di Giambenedetto et al., 2020 [61]
	Tocilizumab (USA)	Lopinavir/ritonavir, ribavirin, and hydroxychloroquine. with a propofol	2 (acute hyper-triglyceridemia)	Improved clinical symptoms	100	Morrison et al., 2020 [62]

the clinical investigation for treatment of COVID-19. Type 1 interferons (IFN—I) is a class of cytokines secreted prominently by plasmacytoid dendritic cells after recognition of PAMPs [31] IFN-I is one of the initial cytokines induced in viral infection. These secreted INFs are recognized by the plasma membrane receptor namely INFAR and induces phosphorylation and translocation of transcriptional factors such as STAT1 into the nucleus. This leads to activation of interferon-stimulated genes (ISG) which are primarily involved in most of inflammatory signaling pathways and immunomodulatory effect. ISG, through an array mechanism, hinder viral replication, interfere with cell metabolism and reduce cytokine secretion and activate adaptive immune responses. Furthermore, the antiviral effect is produced through mitigation of viral fusion and entry, by sensitizing the cells towards pathogen and hence reduce membrane fluidity [32,33]. Recent Chinese guidelines recommended IFNα in combination with antiviral drugs (ribavirin) for treatment of COVID-19 [34]. Interferon therapy with Chinese traditional medicines, antibacterial, antiviral, and corticosteroids was found to enhance the clinical outcome in 135 COVID-19 patients. The recruited population had a median age of 47 years, no significant gender differences with clinically ill to severely ill patients (cardiovascular diseases and malignancy). The study revealed remarkable improvement in patients and reported the death of one patient. The findings showed improved oxygen saturation, lymphocyte, CD4+ T, CD8+ T, B cell, and NK cell counts; also, CT scan advocated resolved GGOs inpatient after treatment with interferons [35]. An open randomized phase 2 trial carried out in Hong Kong involving triple combination therapy viz. interferon beta-1b, lopinavir-ritonavir, and ribavirin were provided to 86 patients, who were tested positive to COVID-19. The result showed that triple combination therapy significantly reduced the viral load, subsided symptoms completely and IL-6 levels within 4 days. In conclusion, it was stated that the therapy appreciably reduces virus shedding duration, shortens hospitalization of patients, alleviates cytokine response and resolves lung GGOs [36]. In another study, 158 randomized and 79 placebo-controlled patients were enrolled in the double-blind multicentre trial at ten hospitals in National Clinical Research Center for Respiratory Diseases, China. The patients received remdesivir and concomitant lopinavir-ritonavir regimen, interferons, and corticosteroids for the treatment of COVID-19. The findings depicted that remdesivir with interferon regimen significantly improved clinical symptoms, relieved fever, improved oxygen saturation, reduced respiration rate and also suppressed cough [37].

In an investigation conducted at the Ningbo Women and Children's Hospital, China, clinical outcome of INF-alpha along with concomitant use of lopinavir-ritonavir was assessed in 36 children with a mean age of 8.3 years. The study displayed improved clinical manifestations in terms of fever, cough, tachypnoea, congestion, sore throat, vomiting, and diarrhea. Serum level of the immune cells were significantly increased; CT scan showed resolved pulmonary GGOs as well as improved oxygen saturation [38]. A phase two multi-center randomized controlled trial carried out at Golestan University of Medical Sciences, Iran involved 105 critically ill COVID-19 patients, who were treated with a combination of interferon-beta, dexamethasone, and immunoglobulin. Main outcome of the trial showed improvement in clinical symptoms, SpO2 level was increased, further, the hospitalization of patients was shortened and the patient did not require mechanical ventilation [39].

In a study, COVID-19 positive multiple sclerosis patient was treated with interferon along with hydroxychloroquine, azithromycin, and enoxaparin sodium at Ankara City Hospital, Ankara, Turkey. This single patient study showed that the combined regimen successfully enables recovery from SARS-2 infection. The patient did not show any symptoms; also, normal respiration, normal levels of WBC, hemoglobin, CRP, platelet count, liver/kidney function parameters were observed [40].

A recent non-controlled trial investigation involved 20 COVID-19 positive patients, who were treated with subcutaneous administration of IFN-β-1a every alternate day along with conventional hydroxychloroquine, and lopinavir/ritonavir treatment. The primary outcomes achieved were subsided symptoms like fever, cough, chest pain, headache, diarrhea, and sore throat. The secondary outcomes were resolved GGOs, reduced ICU stay, and mortality rate [41] Administration of IFN-α2b alone or along with arbidol remarkably mitigated the viral load in the upper respiratory tract (Table 1) [42].

Monoclonal antibodies (mAbs)

Immunopotentiation through active or passive immunization strategies have proven beneficial against a gamut of viral infections, as observed in our previous study and the reports of other research groups [43—45]. Specifically, passive immunization with antibodies is a well-known strategy in the treatment of infectious diseases. But, the specific monoclonal antibodies (mAbs) are highly potent in neutralization of circulating antigen/antigen toxins and amelioration of microbial infection. These monoclonal antibodies have shown effective prophylaxis against severe viral infections like hepatitis, rabies, measles, smallpox, varicella zoster and currently emerged SARS, etc. Many mAbs particularly get associated with the receptor binding domain (RBD) of the spike (S) protein and interferes with receptor binding. While some of mAbs bind with N terminal of RBD epitopes and neutralize the virus with or without inhibiting receptor binding in SARS-CoV. MAb 201 was evaluated for its clinical efficacy against SARS-CoV in golden Syrian hamsters. Results showed that mAb 201, when administered prophylactically prevents viral replication; also, the viral burden was reduced by $10^{2.4}$—$10^{3.9}$ and associated interstitial pneumonitis was ameliorated [46]. A new monoclonal antibody tocilizumab (IL-6 receptor inhibitor) was used for the treatment of COVID-19 in Iceland in a patient with severe respiratory symptoms and fatigue (Table 1). The study results showed improvement in clinical symptoms, oxygen saturation levels and minimum cytokine burst, and importantly the patient did not require endotracheal intubation [47]. Another clinical investigation of tocilizumab against COVID-19 in 20 patients at Anhui Provincial Hospital and Anhui Fuyang Second People's Hospital showed improvement in symptoms of patients as fever was returned to normal, oxygen demand was reduced in 75% patient. More than 90% of patients showed reduction in lung lesion in the CT scan report.

Besides, reduced lymphocyte level and elevated C-reactive protein were also normalized in the tocilizumab-treated patients. The data showed that tocilizumab, along with routine therapy with antiviral and broad-spectrum antibiotics, improved clinical outcomes in severe COVID-19 patients without any adverse effect [48]. Another study involving fifteen patients (12 males and 3 females) with COVID-19 admitted at Zhongfaxincheng campus of Tongji Hospital in Wuhan, China for clinical investigation of tocilizumab treatment. Tocilizumab was administered with and without prednisolone treatment and evaluated for C-reactive protein, IL-6 and clinical outcomes before and after treatment. Results showed that treatment with Tocilizumab attenuated ''cytokine burst'', reduced C-reactive protein and mitigated the inflammatory responses. Unfortunately, ill and critical patient death was occurred during the tocilizumab treatment and needs further investigation in large number of COVID-19 patients [49]. Leronlimab a product of CytoDyn Inc. was investigated in 10 COVID-19 patients with severe illness. Treatment with leronlimab showed rapid reduction in IL-6 levels, restoration of CD4/CD8 ratio, reduction in plasma viremia. This result underscores that treatment with leronlimab restores immunological deficiencies and resolves inflammatory responses [50]. The new ACE-MAB by Sorrento and Mabpharm is in pipeline and under clinical trial against treatment of COVID-19. ACE-MAB is a bi-specific fusion protein with two arms, one comprises human antibody targeting SARS-CoV-2 spike protein whereas another is a truncated ACE2 protein that binds to the spike protein epitope. This fusion selectively blocks the interaction between RBD and CD147, and attenuates inflammation and cytokine burst [51]. Gimsilumab, a product of Roivant Sciences and Mavrilimumab of Kiniksa Pharmaceuticals are granulocyte-monocyte colony-stimulating factor inhibitors and could be effective in treating SARS-CoV-2 [52—54]. Siltuximab, an interleukin (IL)-6 receptor antagonist found clinical significance in COVID-19 patients [55]. CEL-SCI corporation's biotech product LEAPS (ligand antigen epitope presentation system), a cell modulation peptide and an immunomodulator administered via epitope delivery technology to activate cell-mediated T-cell immune response against infection and viral burden reduction [56]. Beyond Spring group has submitted a provisional U.S. patent application for BPI-002, a novel oral small molecule and a T-cell co-stimulator against COVID-19 [57]. mAbs including infliximab or adalimumab are anti-TNF antibodies with remarkable efficacy, broad spectrum of safety and wide availability [58]. A 60-year-old clinically ill patient with multiple myeloma working in Wuhan was admitted to the Hospital of USTC, Hefei, China and treated with tocilizumab along with moxifloxacin and arbidol. After following the treatment protocol significant progress was reported viz. improved oxygen saturation and breathing, chest tightness disappeared, decreased IL-6 level, normal lymphocyte count, and resolved ground-glass opacities. The effect of tocilizumab was mediated through antagonizing the IL-6 receptor and avoiding cytokine storm. The patient found COVID-19 negative and was discharged from the hospital [57]. 100 COVID-19 positive, hyperinflammatory syndrome (HIS) patients were enrolled at Spedali Civili University Hospital in Brescia (Italy). An intravenous infusion of tocilizumab (8 mg/kg) was administered every 12 hours for 11 days. The reported outcomes were improvement in acute respiratory failure, resolved diffuse bilateral opacities, and attenuated symptoms of COVID-19. Unfortunately, 24% of patients died and 2 patients reported adverse effects of tocilizumab viz. septic shock and gastrointestinal perforation [58].

A case study of COVID-19 positive patients with sickle cell syndrome was successfully treated with tocilizumab. The research report showed progressive improvement in general condition, radiological examination, and SpO2 was observed as 97%. [59]. Another case study of COVID-19 positive patient with a history of kidney transplant was successfully treated with a combined regimen of tocilizumab and hydroxychloroquine. The clinical outcomes underscored that after treatment with tocilizumab, the fever was absent, with oxygen saturation of 95%, reduced respiration rate, and normalized WBC count. Radiological examination showed normal lungs and patient was discharged [60].

The single-center study involved 15 COVID-19 positive patients (2 moderately ill, 6 seriously ill and 7 were critically ill) and treated with tocilizumab at Zhongfaxincheng campus of Tongji Hospital in Wuhan, China. The laboratory findings reported that CRP levels in all 15 patients were found normal after treatment with tocilizumab and methylprednisolone. Also, decreased inflammatory activity, and IL-6 level was noted; besides, 6 patients displayed improved/stabilized clinical symptoms. In 4 patients, disease aggravation was observed and the death of 5 patients was reported [61].

Another recent investigation involved 3 clinically ill patients, treated with tocilizumab in combination with the conventional regimen (lopinavir/ritonavir plus hydroxychloroquine) in an Italian Hospital. The clinical outcome in the first hypertensive patient, reported an absence of fever, improvement in the PaO2-to-Fio2 ratio, and CRP was found normal. In the second patient progressive results were obtained and reported as an improvement in the clinical condition, absence of fever, and rapid reduction in CRP. The third patient also showed similar results as an improved clinical condition, oxygen saturation, and resolved fever [49].

Two COVID-19 positive patients with acute hypertriglyceridemia were treated with tocilizumab along with lopinavir/ritonavir, ribavirin, hydroxychloroquine at Henry Ford Hospital, Michigan, USA. The investigational outcome reported that tocilizumab is a potential treatment option in patients with severe COVID-19 (Table 1) [62]. In addition to these interventions, IFN-k plus TFF2 with standard care [63] and type 1 IFN [64] based strategies are proposed to be effective in the management of COVID-19. However, large-scale clinical trials are warranted to ascertain the efficacy of these treatment options in various patient population in terms of severity, ethnicity, genetic aberrations, and other influential factors.

Conclusion

Considering the limitations of current pharmacotherapy employing antivirals, antibiotics, anti-malarials, corticosteroids, and artificial oxygenation, it is imperative to tap for another promising approach against COVID-19 treatment. Extensive literature review and clinical investigations advocated that modulation of immune response could be a highly promising line of attack to combat viral infection like

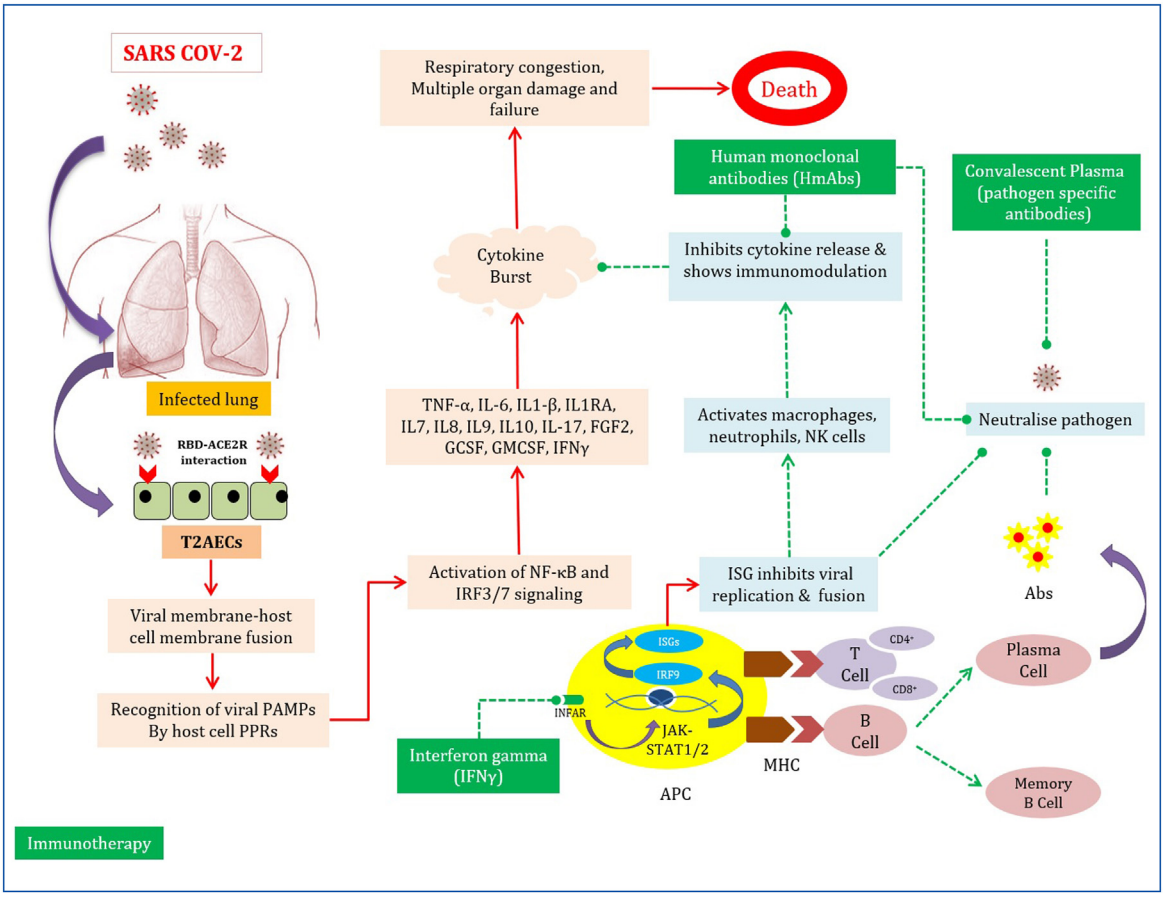

Figure 1. Pathological signaling cascade of SARS-CoV-2 infection and mechanisms of action of various immunotherapeutics including convalescent plasma, interferon gamma (IFNγ) and human monoclonal antibodies.

COVID-19. Modulation of immune response with an infusion of CP proffers appreciable effectiveness, as it contains viral-specific antibodies to effectively eradicate and neutralize circulating pathogens. Treatment with natural proteins like INF, secreted by defense cells is also an interesting strategy to thwart cytokine burst and associated organ damage, which is very common in COVID-19 patients. Human mAbs are more promising advanced approach in the picture to fight against viral survival/replication in the host. Target specific modulation and activation of immune cells like $CD4^+$/$CD8^+$ cells are demonstrated to be effective measures in curtailing the symptoms of COVID-19 via eradication of circulating pathogens as well as reduction of viremia. Collectively, immunotherapeutic modalities act through multiple pathways involving direct pathogen neutralization, inhibition of viral fusion/replication, attenuation of cytokine burst against SARS-CoV-2 infection (Fig. 1). In conclusion, immunotherapy might be used as a stand-alone modality for treating COVID-19 patients. However, based on the demographic and clinical profiles (e.g., disease severity, comorbidities, etc.) of the patients, the physician need to decide up on the use of specific immunotherapy: as a stand-alone therapy or as a vital component in a multimodal regimen. Nevertheless, future investigations are warranted to address the precise (re)purposing of immunotherapeutics for treating specific patient pool in the COVID-19 spectrum.

Acknowledgments

The authors are thankful to Vels Institute of Science, Technology & Advanced Studies (VISTAS), for the facilities extended.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497—506.
[2] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94(7):e00127—220.
[3] Jaimes JA, Millet JK, Stout AE, André NM, Whittaker GR. A tale of two viruses: the distinct spike glycoproteins of feline coronaviruses. Viruses 2020;12(1):83.
[4] de Wit E, Doremalen VN, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016;14(8):523—34.

[5] Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 2020;38(1):1—9.
[6] Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor fedratinib. J Microbiol Immunol Infect 2020;53(3):368—70.
[7] Kindler E, Thiel V, Weber F. Interaction of SARS and MERS coronaviruses with the antiviral interferon response. Adv Virus Res 2016;96:219—43.
[8] Perlman S, Dandekar AA. Immunopathogenesis of coronavirus infections: implications for SARS. Nat Rev Immunol 2005;5(12):917—27.
[9] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017;39(5):529—39.
[10] Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet 2015;386(9997):995—1007.
[11] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433.
[12] Wang LS, Wang YR, Ye DW, Liu QQ. Review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents 2020:105948, http://dx.doi.org/10.1016/j.ijantimicag.2020.105948.
[13] Kikkert M. Innate immune evasion by human respiratory RNA viruses. J Innate Immun 2020;12(1):4—20.
[14] Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-1919. N Engl J Med 2020;382(25):2411—8.
[15] Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;323(24):2493—502.
[16] Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130(4):1545—8.
[17] Virdi V, Depicker A. Role of plant expression systems in antibody production for passive immunization. Int J Dev Biol 2013;57(68):587—93.
[18] Burnouf T, Seghatchian J. Ebola virus convalescent blood products: where we are now and where we may need to go. Transfus Apher Sci 2014;51(2):120—5.
[19] Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: systematic review. Med Virol 2020, http://dx.doi.org/10.1002/jmv.25961.
[20] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323(16):1582—9.
[21] Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020;117(17):9490—6.
[22] Rojas M, Rodriguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, et al. Convalescent plasma in COVID-19: possible mechanism. Autoimmun Rev 2020:102554.
[23] Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan. China. J Med Virol 2020;92(10):1890—901.
[24] Eckhardt CM, Cummings MJ, Rajagopalan KN, Borden S, Bitan ZC, Wolf A, et al. Evaluating the efficacy and safety of human anti-SARS-CoV-2 convalescent plasma in severely ill adults with COVID-19: A structured summary of a study protocol for a randomized controlled trial. Trials 2020;21(1):499.
[25] Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci 2020;35(14):e149.
[26] Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, et al. Treatment of COVID-19 patients with convalescent plasma in Houston, Texas. Am J Pathol 2020;190(8):1680—90.
[27] Chen B, Xia R. Early experience with convalescent plasma as immunotherapy for COVID-19 in China: knowns and unknowns. Vox Sang 2020;115(6):507—14.
[28] Bobek I, Gopcsa L, Réti M, Bekő G, Hancz L, Lakatos B, et al. Successful administration of convalescent plasma in critically ill COVID-19 patients in Hungary: the first two cases. Orv Hetil 2020;161(27):1111—21.
[29] Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev 2001;14(4):778—809.
[30] Liu YJ. IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu Rev Immunol 2005;23:275—306.
[31] Schneider WM, Chevillotte MD, Rice CM. Interferon-stimulated genes: a complex web of host defenses. Annu Rev Immunol 2014;32:513—45.
[32] Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N, Florence AD, et al. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res 2020;178:104791.
[33] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020;14(1):58—60.
[34] Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020;92(7):797—806.
[35] Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir—ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020;395(10238):1695—704.
[36] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569—78.
[37] Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020;20(6):689—96.
[38] Abdolahi N, Kaheh E, Golsha R, Khodabakhshi B, Norouzi A, Khandashpoor M, et al. Letter to the editor: efficacy of different methods of combination regimen administrations including dexamethasone, intravenous immunoglobulin, and interferon-beta to treat critically ill COVID-19 patients: a structured summary of a study protocol for a randomized controlled trial. Trials 2020;21(1):549.
[39] Gemcioglu E, Davutoglu M, Ozdemir EE, Erden A. Are type 1 interferons treatment in multiple sclerosis as a potential therapy against COVID-19? Mult Scler Relat Disord 2020;42:102196.
[40] Dastan F, Nadji SA, Saffaei A, Marjani M, Moniri A, Jamaati H, et al. Subcutaneous administration of Interferon beta-1a for COVID-19: a non-controlled prospective trial. Int Immunopharmacol 2020;85:106688.
[41] Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, et al. Interferon-α2b treatment for COVID-19. Front Immunol 2020;11:1061.
[42] Sivakumar SM, Sukumaran N, Nirmala L, Swarnalakshmi R, Anilbabu B, Siva L, et al. Immunopotentiation of hepatitis B vaccine using biodegradable polymers as an adjuvant. J Microbiol Immunol Infect 2010;43(4):265—70.
[43] Raghunandan R, Lu H, Zhou B, Xabier MG, Massare MJ, Flyer DC, et al. An insect cell derived respiratory syncytial virus (RSV) F nanoparticle vaccine induces antigenic site II antibodies and protects against RSV challenge in cotton rats by active and passive immunization. Vaccine 2014;32(48):6485—92.

[44] Walker LM, Burton DR. Passive immunotherapy of viral infections: 'super-antibodies' enter the fray. Nat Rev Immunol 2018;18(5):297—308.
[45] Roberts A, Thomas WD, Guarner J, Lamirande EW, Babcock GJ, Greenough TC, et al. Therapy with a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody reduces disease severity and viral burden in golden Syrian hamsters. J Infect Dis 2006;193(5): 685—92.
[46] Bjornsson AH, Olafsdottir T, Thormar KM, Kristjansson M, Thorisdottir AS, Ludviksson BR, et al. First case of COVID-19 Treated with Tocilizumab in Iceland. Laeknabladid 2020;106(5):247—50.
[47] Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 2020;117(20):10970—5.
[48] Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol 2020;92(7):814—8.
[49] Patterson BK, Seethamraju H, Dhody K, Corley MJ, Kazempour K, Lalezari JP, et al. Disruption of the CCL5/RANTES-CCR5 pathway restores immune homeostasis and reduces plasma viral load in critical COVID-19. medRxiv 2020, http://dx.doi.org/10.1101/2020.05.02.20084673.
[50] Lythgoe MP, Middleton P. Ongoing clinical trials for the management of the COVID-19 pandemic. Trends Pharmacol Sci 2020;41(6):363—82.
[51] Nold C, Vella A. (inventors) University of Connecticut (assignee). Inhibiting granulocyte macrophage-colony stimulating factor (gm-csf) prevents preterm birth. United States patent application US 16/655,733; 2020. Apr 23. https://www.freepatentsonline.com/20200123246.pdf. [Accessed October 22, 2020 (28 pp.)].
[52] Crotti C, Agape E, Becciolini A, Biggioggero M, Favalli EG. Targeting granulocyte-monocyte colony-stimulating factor signaling in rheumatoid arthritis: future prospects. Drugs 2020;79(16):1741—55.
[53] Cabana JA. Altasciences completes phase I study on gimsilumab for ARDS in COVID-19. Altasciences 2020. https://www.altasciences.com/press-release/altasciences-completes-phase-i-study-imsilumab-ards-covid-19. [Accessed October 22, 2020].
[54] Gritti G, Raimondi F, Ripamonti D, Riva I, Landi F, Alborghetti L, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. medRxiv 2020, http://dx.doi.org/10.1101/2020.04.01.20048561.
[55] Philippidis A. COVID-19: top 60 drug treatments in development: the biopharma industry is ramping up the development of dozens of potential drug therapies and clinical testing in an all-hands effort to combat the pandemic. Genet Eng Biotechnol News 2020;40(4):10—3.
[56] Zhang X, Song K, Tong F, Fei M, Guo H, Lu Z, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv 2020;4(7):1307—10.
[57] Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev 2020;19(7):102568.
[58] De Luna G, Habibi A, Deux JF, Colard M, d'Orengiani PH, Schlemmer F, et al. Rapid and severe Covid-19 pneumonia with severe acute chest syndrome in a sickle cell patient successfully treated with tocilizumab. Am J Hematol 2020;95(7):876—8.
[59] Fontana F, Alfano G, Mori G, Amurri A, Tei L, Ballestri M, et al. Covid-19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab and hydroxychloroquine. Am J Transplant 2020;20(7):1902—6.
[60] Di Giambenedetto S, Ciccullo A, Borghetti A, Gambassi G, Landi F, Visconti E, et al. Off-label use of tocilizumab in patients with SARS-CoV-2 infection. J Med Virol 2020, http://dx.doi.org/10.1002/jmv.25897.
[61] Morrison AR, Johnson JM, Ramesh M, Bradley P, Jennings J, Smith ZR. Letter to the Editor: Acute hypertriglyceridemia in patients with COVID-19 receiving tocilizumab. J Med Virol 2020, http://dx.doi.org/10.1002/jmv.25907.
[62] Zhang Q, Bastard P, Liu Z, Pen JL, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 2020, http://dx.doi.org/10.1126/science.abd4570.
[63] Fu W, Liu Y, Liu L, Hu H, Cheng X, Liu P, et al. An open-label, randomized trial of the combination of IFN-κ plus TFF2 with standard care in the treatment of patients with moderate COVID-19. EClin Med 2020:100547.