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Review

Prevention and treatment of COVID-19: Focus on interferons, chloroquine/hydroxychloroquine, azithromycin, and vaccine

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ABSTRACT

The ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has drawn the attention of researchers and clinicians from several disciplines and sectors who are trying to find durable solutions both at preventive and treatment levels. To date, there is no approved effective treatment or vaccine available to control the coronavirus disease-2019 (COVID-19). The preliminary *in vitro* studies on viral infection models showed potential antiviral activities of type I and III interferons (IFNs), chloroquine (CQ)/hydroxychloroquine (HCQ), and azithromycin (AZM); however, the clinical studies on COVID-19 patients treated with CQ/HCQ and AZM led to controversies in different regions due to their adverse side effects, as well as their combined treatment could prolong the QT interval. Interestingly, the treatment with type I IFNs showed encouraging results. Moreover, the different preliminary reports of COVID-19 candidate vaccines showcase promising results by inducing the production of a high level of neutralizing antibodies (NAbs) and specific T cell-mediated immune response in almost all participants. The present review aims to summarize and analyze the recent progress evidence concerning the use of IFNs, CQ/HCQ, and AZM for the treatment of COVID-19. The available data on immunization options to prevent the COVID-19 are also analyzed with the aim to present the promising options which could be investigated in future for sustainable control of the pandemic.

1. Introduction

In less than one year, the pandemic of coronavirus disease-2019 (COVID-19) has killed more than 1,193,755 out of over 45,899,858 people infected in the world, as of October 31th, 2020 [1]. To date, no antiviral therapy or vaccines are available against COVID-19; nevertheless, scientists around the world are mobilized to identify the treatment candidates and vaccines. To date, several solutions have been proposed, involving the use of existing antivirals, antibiotics, and anti-inflammatory drugs with known features such as optimal dosage and pharmacokinetics in the therapeutic strategies, for the treatment of COVID-19 [2–4]. Most strategies considered in the clinical trials aim to accelerate the viral clearance and inhibit the cytokine storm to minimize the need for mechanical ventilation, long hospital stays, and COVID-19 associated mortality. To date, different anti-inflammatory drugs such as tocilizumab, chloroquine (CQ)/hydroxychloroquine (HCQ), and dexamethasone have been proposed to decrease or suppress the release/-production of pro-inflammatory cytokines with the aim to minimize the cytokine storm associated with SARS-CoV-2 [5,6]. Several clinical trials are underway; however, none of the drugs has been consistently proven significantly effective (Fig. 1) [7–10]. Among the trials of using different drugs, the use of CQ/HCQ in combination with azithromycin (AZM) has the highest numbers of trials and patients [7]. *In vitro* studies have shown the effectiveness of CQ/HCQ and AZM as antiviral and

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anti-inflammatory drugs [4,11–13]. In addition, there are specially approved treatment strategies for urgent use during the COVID-19 pandemic despite the lack of substantial data. These emergency treatment strategies include the use of remdesivir and convalescent plasma in the USA and favipiravir in China [14–16]. Along with trials of different treatment options, several vaccine candidates are under evaluation. An effective vaccine could ultimately reduce the person-to-person transmission, viral shedding, and disease severity [17].

Likewise in earlier viral outbreaks, some patients recover without any treatment at account of effective immune system, including the innate immunity, cell-mediated immunity, and humoral immunity [18]. Such patients either have an effective primary immune response or a secondary immune response due to previous contact with a pathogen showing similar epitopes with SARS-CoV-2 [19]. The use of drugs that can restore, strengthen, and modulate the immune system is, therefore, a perfect approach in handling the COVID-19. The immune response against human coronaviruses (HCoVs), including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6,20–24] and severe acute respiratory syndrome coronavirus (SARS-CoV) [25–28], is characterized in most cases by low levels of type I and III interferons (IFNs) resulting in reduced innate response despite the excessive production of pro-inflammatory cytokines (cytokine storm). Although the IFNs effectors' pathways are not affected by HCoVs, it makes sense to consider exogenous IFNs as therapeutic options which could increase the body's response to the infecting virus. This strategy is already in use considerable success in treating viral infections such as hepatitis viruses [29,30]. In fact, the IFNs stimulate the important factors of innate immunity, that is an essential pivot of host defense against viruses and intracellular pathogens [29,30].

This review aims to describe and summarize the recent progress evidence concerning the use of IFNs, CQ/HCQ, and AZM for the treatment of COVID-19. We highlight the importance of IFNs in the treatment of COVID-19 and describe the modalities of the immune response protection against coronaviruses, including SARS-CoV, SARS-CoV-2, and MERS-CoV viruses.

2. Interferons and coronaviruses

Interferons (IFNs) are important cytokines which orchestrate the immune response to pathogens such as fungi, bacteria, and viruses. The production of IFNs is triggered by the recognition of pathogenic components through pattern-recognition receptors (PRR) [31]. The types I

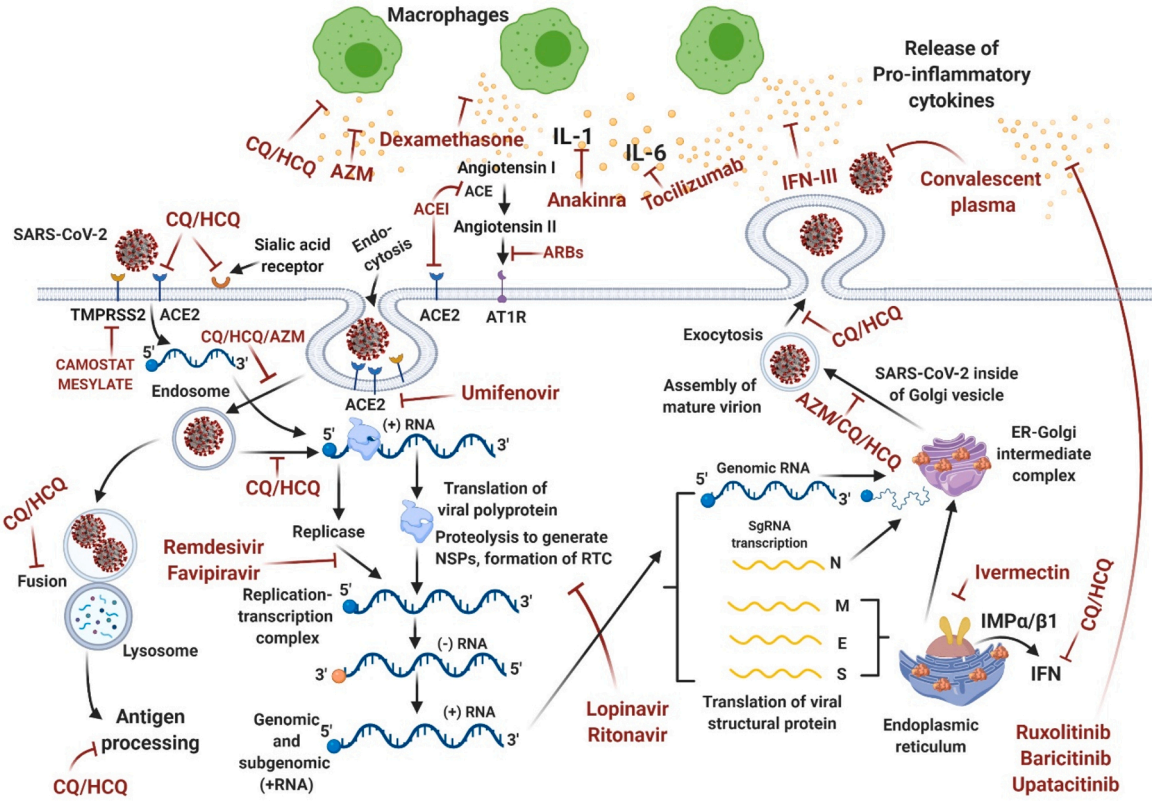

Fig. 1. Illustration of replication mechanism and potential drug targets of SARS-CoV-2. The SARS-CoV-2 infects the host cell in two ways: either through the plasma membrane or endosomes or through the interaction between its spike protein (S) and cell receptor, ACE2. The SARS-CoV-2 may also enter the host cell through the interaction between its S protein and sialic acid receptors. The TMPRSS2 close to the ACE receptor activates the S protein in the endosome *via* followed by initiating the fusion of the SARS-CoV-2 membrane with the plasma membrane. The viral RNA is released and translated in the viral polyprotein followed by proteolysis to produce non-structural proteins (NSPs) and form a replication-transcription complex (RTC). The RTC drives the synthesis of (-) RNA. The full length (-) RNA copies of the genome provide the templates for full-length (+) RNA genomes. The transcription further produces a subset of subgenomic RNAs, including those encoding the accessory and structural proteins. The translated structural proteins (M, N, E, and S) and the genomic RNA are assembled into the viral nucleocapsid and envelope in the ER-Golgi intermediate compartment, which is subsequently released *via* exocytosis. The potential drug targets are shown in red such as inhibitors of viral entry to human cells: chloroquine (CQ)/hydroxychloroquine (HCQ), umifenovir; viral protease inhibitor: lopinavir/ritonavir, ivermectin; RNA-dependent RNA polymerase inhibitor: remdesivir, favipiravir; interleukin (IL)-6 inhibitor; IL-1 inhibitor: anakinra; Janus kinases inhibitor: baricitinib, ruxolitinib, upadacitinib; corticosteroid: dexamethasone; an inhibitor of the cellular serine protease TMPRSS2: camostat mesylate; antimicrobial/antibiotics: azithromycin (AZM); immunoglobulins: convalescent plasma; interferons (IFNs); angiotensin-converting enzyme inhibitor (ACEI); angiotensin II receptor blocker (ARB). Abbreviations: ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane protease serine 2; AT1R, angiotensin II type 1 receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RNA, ribonucleic acid; (+) RNA, Positive-strand (5′-to-3′) RNA; (-) RNA, negative-strand (3′-to-5′) RNA; N, nucleocapsid protein; M, matrix protein; E, envelope protein; S, spike protein.

(IFN-α, IFN-β, IFN-ω, IFN- ε et IFN-κ) and III (IFN- λ1, IFN- λ2, IFN- λ2, IFN- λ4) IFNs are involved in the innate antiviral response in most cells, while type II INF (IFN-γ) predominantly serves as the communication molecule between the specialized cells of the immune system [32,33]. Essentially produced by the plasmacytoid dendritic cells (pDC), the type I IFNs target the heterodimeric receptor (IFNAR) [31–33]. The IFN-λ molecules are expressed by certain myeloid and epithelial cells and thought to produce similar effects with type I IFNs. The growing evidence suggests that IFN-λ plays a non-redundant role in promoting the innate immunity and stimulating the adaptive immune response to viral pathogens [34]. IFN-λ induces a non-specialized state of antiviral resistance and uses the same transduction pathway as type I IFNs, although through a different receptor (IFNLR) [35].

IFNs activate hundreds of genes known as IFN-stimulated genes (ISGs) through the Janus kinase-signal transducer/activator of transcription (JAK/STAT) signaling pathway, which provides a complete antiviral response targeting all stages of viruses' replicative cycles [32,36]. For example, MX2 (the IFN-induced GTP-binding protein) prevents the replication of human immunodeficiency virus (HIV) after its association with the capsid [37] and IFITMs (IFN-induced transmembrane protein) probably modify the membrane structure and the pH of endosomes by inhibiting the fusion of viral membranes with the cell membrane [38]. In addition to many roles in regulating the immune response [38], it is demonstrated that IFITM proteins prevent the entry of SARS-CoV and MERS-CoV into the cell [39,40]. Similarly, ISG15 binds and inactivates certain viral proteins [41], while tetherin inhibits the release of viral particles by sequestering them on the membrane of infected cells [42]. IFNs also activate other genes that lead to the overexpression of PRRs to increase the alertness of cells to pathogens or inhibit the translation of new proteins, thus reducing the production of new viral particles [32,36]. Moreover, IFNs can induce apoptosis of infected cells and modulate the adaptive immune response [32,36]. Thus, IFN-α and β participate in the differentiation of certain T lymphocytes, while IFN-λ intervenes in the maturation of T and B lymphocytes [32,36]. The response of IFN could be affected by the viral factors as well as the host factors such as the age [43,44]. The antiviral response mediated by the IFNs depends on the viral load. A low viral load is associated with adequate IFN response which leads to early and effective virus clearance whereas a high virus load delays the IFNs production and lead to inflammation and lung damage [26,45].

The discovery of the effectiveness of IFNs in antiviral control has made it possible to envisage their therapeutic use [33]. The IFN-α and β are mainly used to treat hepatitis viruses because these induce a state of antiviral resistance used in conjunction with other drugs with direct antiviral action [46,47]. In clinical studies, IFN-λ also showed promising results against chronic hepatitis viruses [48–50]. Many viruses inhibit the production of IFNs by acting on the JAK/STAT signaling pathway [51,52]. As for coronaviruses, these use various strategies to escape the antiviral response of the innate immune system [52,53]. The HCoVs RNA genome (Fig. 2) consisted of open-reading frames (ORFs) encodes the nonstructural proteins (NSP1-16), structural proteins (nucleocapsid N, membrane M, envelope E, and spike S), and accessory proteins, which target numerous signaling pathways involved in antiviral response (Table 1 and Fig. 3) [54,55]. HCoVs can interfere with the processes of induction of innate immunity, including the recognition of the virus by PRRs, inhibition of IFNs signaling, IFNs production, and ISG effector's function. SARS-CoV avoids its recognition by the PRR either by protecting its PAMPS (viral RNA) or by inhibiting the activation of PRR [56]. To avoid activation of the RIG-I-like receptor (RLR) by dsRNA replication intermediates, the SARS-CoV can replicate inside the double-membrane vesicles [56].

In vitro observations and clinical studies of SARS-CoV patients have shown a deficiency of cytokines, including IFN-α/β and IFN-γ, compared to influenza patients [25]. Specifically, decreased amounts of IFN-α/β and IFN-λ is also reported in COVID-19 patients [22]. Similarly, in mice, SARS-CoV infection induces a low level of IFN-α/β and IFN-λ [27]. Moreover, a study in ferrets has shown that SARS-CoV-2 significantly induces a lower production of IFNs than the Influenza A virus (IAV) [22]. Additionally, the production of IFN-β and ISGs in IAV infection arises more rapidly than in SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) [57]. Thus, a cohort clinical study of Covid-19 patients tested 8–12 days subsequent first symptoms showed a low level of blood type I IFN associated with higher viral load, chemokines, and pro-inflammatory cytokines resulting in decreased innate immunity and COVID-19 progression. The ISGs expression was lower in severe than in mild COVID-19 [20]. In contrast, a study carried out using bronchoalveolar lavage fluid from 8 cases of COVID-19 reported a higher expression of ISGs and pro-inflammatory genes, including chemokines, compared to controls [58]. Clinical studies of SARS-CoV and MERS patients reported that the severity of the disease leads to a high increase in IFNs with the viral load remaining high [59,60].

In vitro studies involving Vero cells showed that SARS-COV-2 exhibits a greater sensitivity to IFN-α/β than SARS-COV; where the viral titers were significantly reduced by over 4 log after IFN-α or IFN-β treatment at 50 IU/Ml [61,62]. Similar results were found with MERS-CoV infected cells [63]. Better viral outcomes were observed in SARS-COV infected macaques after receiving pegylated IFN-α [64]. During IAV infection in mice, IFNs-λ was the predominant IFN type with viral replication control capability without induction of inflammation [65]. IFN-λ plays a role by providing protection against IAV respiratory tract infection. Similarly, *in vitro* studies showed that IFN-λ_4 inhibits the replication of MERS-COV in the respiratory epithelial cells, with higher induction of ISG [66]. Moreover, the use of IFN-β1b decreased the viral load and lung pathology in marmosets infected with MERS-CoV [67]. Similar results were found with MERS-CoV infected macaques after receiving IFN-α2b and ribavirin [68]. Similarly, mycophenolic acid and IFN-β reduced viral load in MERS-CoV infected cells [69]. In contrast, IFN-β associated with lopinavir/ritonavir (LV/RTV) ameliorated the pulmonary function but did not heal the lung pathology in mice infected with MERS-CoV [70].

Vapor inhalation of IFN-α combined with ribavirin was

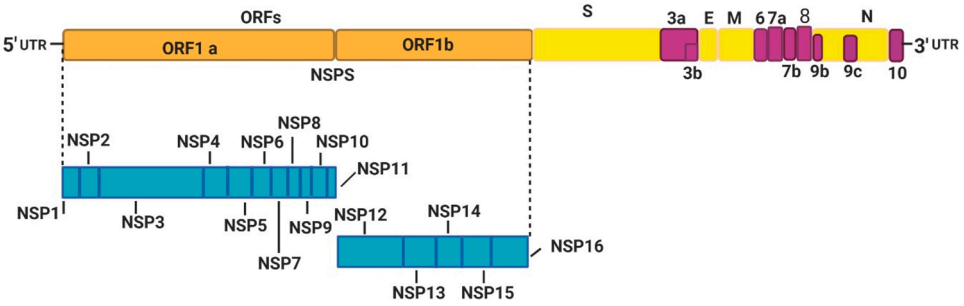

Fig. 2. The SARS-CoV-2 genome and encoded proteins. ORF1a and ORF1b encode the nonstructural proteins (NSP1-16), structural proteins (S, E, M, and N), and accessory proteins (ORF3a, 3b, 6, 7a, 7b, 8, 9b, 9c, and 10). The 5′-UTR and 3′-UTR are untranslated extremities of the genome. NSP, non-structural protein; ORF, open reading frame; UTR, untranslated region.

Table 1
Coronavirus antagonism upstream of interferon induction.

Coronavirus	Mechanism of evasion upstream of IFN signaling	References
SARS-CoV	Viral protein PLP (NSP3) inhibits IFNs production by blocking the nuclear translocation and phosphorylation of IRF3. PLP adversely controls the antiviral immune response by inhibiting the STING signaling.	[84,85,86]
	Viral NP, ORF3b, and ORF6 prevent the TRIM25 activation of RIG-I and inhibit the transcription of ISGs. Viral NP inhibits the IRF3 function.	[87,88,89,90]
	ORF6 antagonizes the STAT1 function.	[91]
	Viral protein NSP14 mimics the 5'cap structure on the viral RNA by its guanine -N7-methyltransferase activity.	[92]
	Viral protein NSP15 acts on negative-sense viral RNA by cleaving its 50-polyuridines.	[93]
	ORF3a induces the degradation of IFNAR1.	[94]
	Viral EP, ORF3a, and ORF8b induce the pro-inflammatory cytokines through NF-κB activation after triggering the NLRP3 inflammasome.	[95,96,97,98]
	ORF3b suppresses the induction of type I IFNs by acting on IRF3 or MAVS.	[99]
SARS-CoV-2	Viral protein NSP15 inhibits the induction of IFNs production by interacting and closing the signaling RIG-I/MAVS and IRF3.	[55]
	Viral protein NSP15 interacts with RNF41, an activator of IRF3 and TBK1. The viral protein NSP13 interacts with the signaling transitional TBK1 that mediates the production of IRF3. NSP13 antagonizes the NF-kB pathway.	[55]
	Viral protein NSP10 induces the production of cytokine storm by facilitating the IL-8 induction after interacting with NKRF.	[100]
	ORF6 inhibits nuclear export of host mRNA by targeting the NUP98-RAE1 complex.	[55]
	ORF9c antagonizes the NF-kB pathway.	[55]
	ORF, 4a, 4b, and 5 inhibit the nuclear translocation of IRF3 and induce the suppression of IFNs production.	[101]
MERS-CoV	Viral protein NS4a is a type I and type III IFNs antagonist, which itself binds to the dsRNA, impedes PKR activation, and inhibits the PACT, an activator of RLRs.	[102,103,104]
	Viral protein NS4b prevents the host RNase L activation, another activator of RLRs.	[105]
	ORF4b protein inhibits the type I IFN production through nuclear and cytoplasmic targets. ORF4b impedes the innate immune response by inhibiting the NF-kB nuclear transport.	[106,107]
	Viral proteins NSP10 and NSP16 protect the viral RNA from MDA5 recognition by modifying the 5' cap structure with its 2'-0-methyltransferase activity.	[108,109]
HCoVs	Viral protein NSP1 inhibits the phosphorylation of STAT1 and host mRNA translation by binding to 40S ribosomal subunit.	[87,88,110,111,112,113]
	ORF9b (except for MERS-CoV) interacts indirectly with the RIG-I/MAVS signaling adapter *via* its association with Tom70, suggesting a preserved mechanism of IFNs escape. ORF9b interacts with the IRF3 signaling pathway.	[55,114]
	Viral MP inhibits the TBK1 signaling and nuclear translocation of IRF3. Viral MP interacts with the innate receptors and signaling molecules to impound them in the cytoplasmic compartments.	[101,115]
	ORF6 (except for MERS-CoV) inhibits the MAVS, TBK1, and IRF3.	[116]

NSP, nonstructural protein; IRF, IFNs regulatory factor; STAT1, signal transducer and activator of transcription 1; ORF, open reading frame; PLP, papain-like protease; ISG, IFN-stimulated genes; TRIM 25, tripartite motif-containing 25; NP, nucleocapsid protein; MP, matrix protein; EP, envelope protein; RIG-I, retinoic acid-inducible gene I; MAVS, mitochondrial antiviral signaling protein; TBK1, tank-binding kinase-1; Tom70, translocase of the mitochondrial outer membrane 70; RNF41, ring finger protein 41; NKRF, NF-Kβ repressing factor; PKR, protein kinase R; RLRs, RIG-I-like receptors; STING, stimulator of interferon genes; PACT, protein activator; RAE1, ribonucleic acid export 1; NUP98, Nucleoporin 98.

recommended in China as guidelines for the treatment of COVID-19 [71,72]. In Hubei province, 2,944 healthcare workers categorized in high-risk and low-risk groups received daily nasal drops of the recombinant human interferon-gamma (rhIFN-α) during 28 days for COVID-19 prevention. The rhIFN-α was combined with thymosin-α1 for the high-risk group. The findings of the study showed the potential of IFN for prevention of COVID-19 [73]. In Hong Kong, the administration of LV/RTV and ribavirin (RV) in addition to subcutaneous injection of IFN β-1b significantly reduced the virus load, symptoms, and the recovery time in COVID-19 patients in comparison to the antiviral drugs used without IFN [74]. In another clinical trial in Wuhan, China on 77 patients with moderate COVID-19, who were administered either oral umifenovir (N = 24), IFN-α2b (N = 7) or a combination of both compounds (N = 46), showed that patients treated with IFN present rapid viral clearance and reduced inflammatory signs compared to others [74]. A retrospective cohort study in Shenzhen city and Hubei province (China) on 141 patients with COVID-19 who inhaled IFN-α2b (N = 70) or a combination of IFN-α2b and umifenovir (N = 71) showed that patients treated with IFN- α2b present rapid SARS-CoV-2 clearance and reduced hospital stay [75]. In a study made in Turkey, the type I IFN associated with HCQ, AZM, and enoxaparin sodium was used to treat COVID-19 patients with multiple sclerosis, which demonstrated a rapid recovered of patients. It was difficult to evaluate the effect of IFN because the patients were treated with other drugs [76]. In the United Arab Emirates, the Pegylated IFN-α-2a was used to treat three patients with severe COVID-19 (2 patients with no significant medical history and one patient was known as types II diabetes mellitus), where the patients recovered with progress in clinical status within 36 h [77]; however, the reliability of the findings of this study is limited because of the small sample size (i.e., n = 3). In a clinical study conducted in Iran, 20 COVID-19 patients received IFN-β-1a in combination with HCQ, and LV/RTV as the treatment [78]. Within 10 days, the viral clearance results showed a significant decrease with the recovery of all patients in 14 days. In a randomized clinical trial (RCT) in Iran, the IFN β-1b reduced the mortality by significantly raising the discharge rate of 33 patients on day 14 compared to the control group comprising of 33 patients treated with LV/RTV or atazanavir/ RTV in combination with HCQ [98]. Furthermore, the inhaled IFN-β-1a reduced the risk of developing severe COVID-19 among 101 patients by 79 % in phase 2 clinical trial (NCT04385095) in the United Kingdom [79].

Overall, these studies demonstrate that despite the inhibition of endogenous IFNs production by HCoVs, the supply of exogenous IFN represents a promising therapeutic approach. An early and suitable administration of IFN-α/β and IFN-λ to COVID-19 patients could be of great value in controlling the viral infection while avoiding inflammation and tissue damage. In animal models, an early IFN administration better protects animals in comparison to the late treatments [28,45,80]. Moreover, IFN-α/β signaling avoids excessive IFN-γ-mediated responses and therefore prevents lung injury and chronic inflammation [81]. IFN-λ is essential for controlling viral replication in the upper respiratory tract [82]. It decreases the viral spread in the lower respiratory tract as well as the transmission to the new hosts. When the virus reaches the lungs due to failed initial viral control, the lungs are protected by IFNs-α/β [65,82,83]. Additionally, the unique quality of the IFN-λ response is long-lasting without inflammatory effects [61]. These features make IFN-λ attractive for COVID-19 prevention and treatment strategies.

3. Chloroquine/hydroxychloroquine, azithromycin, and coronaviruses

Chloroquine (CQ) is a drug indicated in the treatment and prevention

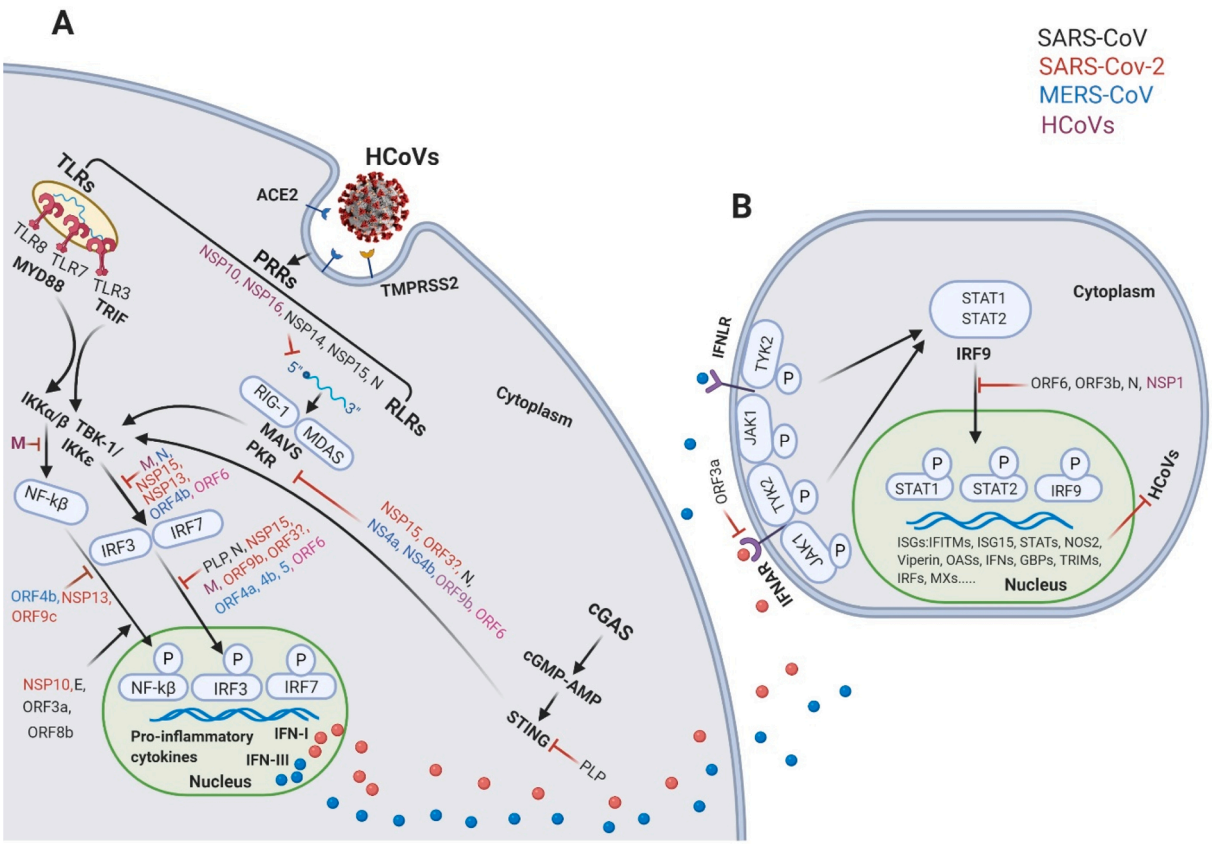

Fig. 3. Schematic illustration of the innate immune response to human coronavirus infection. The HCoVs infect the host cell through interaction between its spike protein (S) and the cell receptor, ACE2. Upon viral RNA recognition, the PRRs activate the innate cellular response reactions that normally lead to the production of pro-inflammatory cytokines and IFNs through NF-kB and IRF3/IRF7 (A). IFNs, secreted in an autocrine and paracrine behavior, induce the expression of ISGs *via* the JAK-STAT signaling pathway involved in antiviral response (B). Some viral proteins such as SARS-CoV's NSP1, PLP, NSP10, NSP13, NSP14, NSP15, ORF3b, and ORF9b proteins and the MERS-CoV's NS4a, NS4b, ORF4a, ORF4b, and ORF5 proteins inhibit this natural response at several levels. See Table 1 for detailed mechanisms at each level.

HCoVs, human coronavirus; PRRs, pattern-recognition receptors; TLRs, toll-like receptors; RIG-I, retinoic acid-inducible gene I; MAVS, mitochondrial antiviral signaling protein; NSP, non-structural protein; IRF, IFNs regulatory factor; STAT, signal transducer and activator of transcription; ORF, open reading frame; PLP, papain-like protease; ISG, IFN-stimulated genes; N, nucleocapsid protein; M, matrix protein; E, envelope protein; TBK1, TANK-binding kinase-1; MyD88, myeloid differentiation primary response 88; TRIF, TIR domain-containing adapter-inducing IFN-β; PKR, protein kinase R; RIG-I, retinoic acid-inducible gene 1; RLRs, RIG-I-like receptors; STING, stimulator of interferon genes; MDA-5, melanoma differentiation-associated protein 5; IkB, inhibitor of nuclear factor kB; IKK-ε, Iκ B kinase-ε; NLRP3, NOD-like receptor family pyrin domain containing 3; IFNAR, interferon alpha and beta receptor; IFNLR, interferon lambda receptor; TRIMs, tripartate motif proteins; P, phosphate; GBPs, guanylate binding proteins; OASs, oligo adenylate synthases; NOS2, nitric oxide synthase 2; IFITMs, IFN-induced transmembrane proteins.

of malaria as well as in rheumatology and dermatology for rheumatoid arthritis and certain lupus [117,118]. It induces the production of reactive oxygen species (ROS)-mediated toxicity in inner glial cells after prolonged treatment requiring the use of vitamin C to prevent the ROS production [119]. High dose of vitamin C inhibits cytokines storm in COVID-19 patients by exerting immunomodulatory properties [120, 121] and induces the production of IFNs in patients with viral infections [122]. Furthermore, vitamin C reduces pulmonary lung inflammation and lung injury due to ROS release by phagocytes (Fig. 4) [26,123]. Hydroxychloroquine (HCQ) is a less toxic drug derived from CQ with similar properties to the latter [124] and used in the management of certain autoimmune diseases, including rheumatoid arthritis and lupus erythematosus [118]. *In vitro* and *in vivo* studies have certified that CQ can inhibit the replication of numerous intracellular microorganisms, including HCoVs, Zika virus, and HIV [4,11,12]. The action of CQ and HCQ may be different depending on the type of microorganisms, but it is shown that it targets the interaction between the SARS-CoV and its receptor by hampering the glycosylation of its cellular receptors blocking the SARS-CoV infections [125]. Besides, CQ/HCQ blocks the sialic acid receptors, thus preventing the entry of SARS-CoV-2 into the upper respiratory tract [126]. Furthermore, CQ has an immunomodulatory ability on activated immune cells [11,127]. It downregulates the expression of TLRs (Toll-like receptors) and TLR-mediated signal transduction and decreases or suppresses the release and production of TNF-α, IL-1, and IL-6, which facilitate the inflammation (cytokines storm) in COVID-19. In fact, CQ inhibits the interactions between TLRs of antigen-presenting cells (APC) and viral nucleic acid, and subsequently prevent the production of IFNs [11,127–129]. CQ (lysosomotropic drug) is also a powerful inhibitor of endosome-lysosome acidification, which allows the development of SARS-CoV and then its processing in the cytosol [11,127]. CQ inactivates all endosomal proteinases and results in APC reduced function; hence, impairing the adaptive immunity [130]. Moreover, CQ inhibits the viral RNA and DNA polymerase, virion assembly, and viral shedding (Fig. 1) [16]. CQ can interact with the LV/RTV in COVID-19 patients, and cause the prolongation of the QT interval [131]. HCQ being less toxic with potent antiviral activity against SARS-CoV-2 compared to the CQ, is preferred for the treatment of COVID-19 [131,132].

Azithromycin (AZM) is the first macrolide antibiotic in the azalide group, which inhibits the synthesis of bacterial proteins, quorum-sensing, and biofilm formation [133,134]. It has an antibacterial mechanism related to that of other macrolides but accumulates more

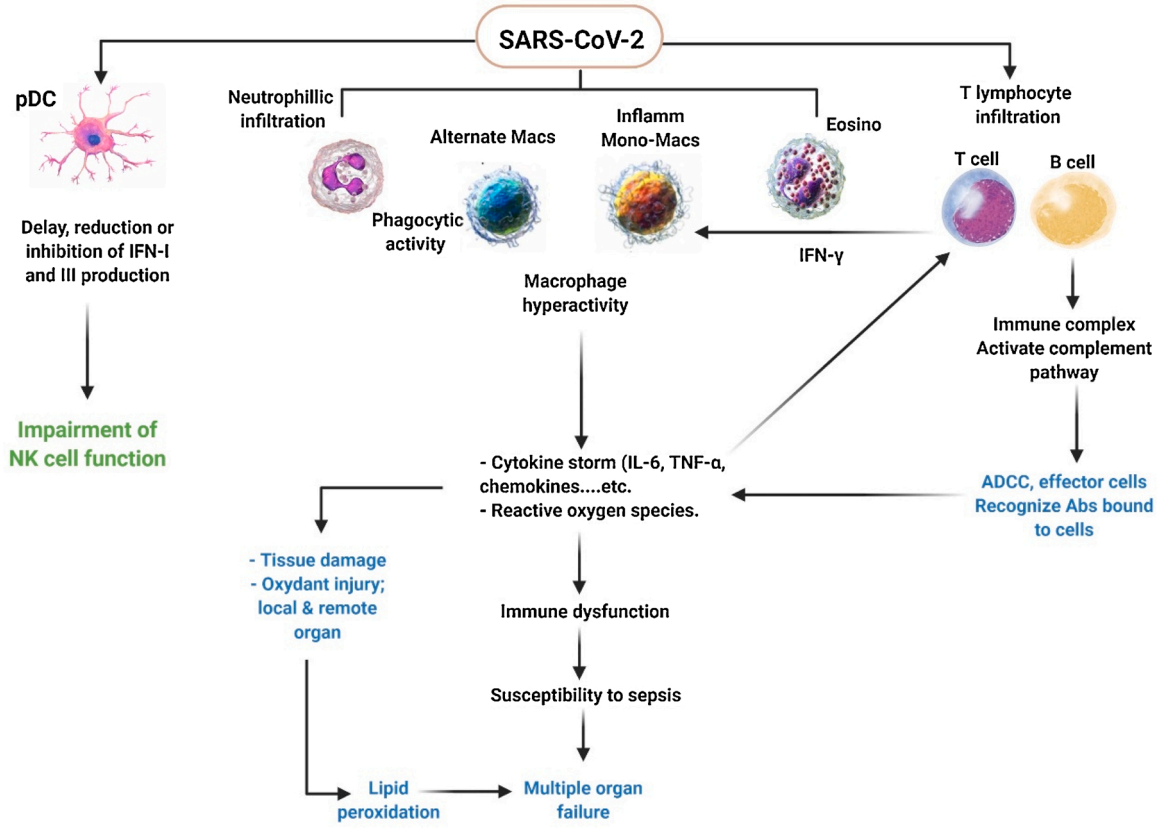

Fig. 4. The immunological response to SARS-CoV-2 infection showing the release of ROS by phagocytes.
pDS, plasmacytoid dendritic cells; IL, interleukin; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma; Inflamm: inflammatory; Eosino, eosinophils; Mono, monocytes; Macs, macrophages; Neutro, neutrophils; NK cell, Natural killer cell; Abs, antibodies; ADCC, Antibody-dependent cell-mediated cytotoxicity; ROS, reactive oxygen species.

effectively in the cells, mainly phagocytes [133]. Recently, AZM has received increasing attention because of additional properties on host-defense reactions by exerting the immunomodulation effects in chronic inflammatory diseases [133,135]. The modulation of immune responses enables the lasting therapeutic advantage of AZM in chronic obstructive pulmonary disease, cystic fibrosis, non-eosinophilic asthma, and non-fibrous cystic bronchiectasis [133]. Macrolides such as AZM present the antiviral properties on bronchial epithelial cells by decreasing the rate of rhinovirus replication in the isolated bronchial cells of cystic fibrosis patients using a mechanism related to IFN induction [136]. AZM is associated with increased expression of PRR, IFN β, IFN λ, and IFN-stimulated genes [136]. It also has antiviral properties against rhinoviruses by decreasing the synthesis of intercellular adhesion molecules such as ICAM-1, which are determinant routes for virus integration [137]. *In vitro* studies have also demonstrated an inhibitory effect of macrolides on the respiratory syncytial virus (RSV) in bronchial epithelial cells [138]. This would be linked to the prevention of interaction with the cellular viral target [138]. AZM also seems to inhibit the Zika virus replication *in vitro* on Vero cells; however, the antiviral action mechanism, in this case, has not been studied [139]. Similarly, AZM has shown *in vitro* activity against the Ebola virus on Vero cells [140]. In *in vitro* model for the influenza virus (H1N1), AZM interferes with the cellular internalization process of the virus [141]; however, the drug must be present before the infection for its maximum efficacy in this model. Macrolides such as AZM and spiramycin have also shown some activity on Enterovirus species in animal models of Enterovirus A71 infection by relieving the symptoms and increasing the animal survival [142]. As a senolytic drug, AZM has the ability to accelerate the phagocytic power of macrophages and selectively kills the senescent cells [143,144]. In a retrospective study on Saudi patients with severe MERS-CoV infection, macrolides used according to different regimens showed a weak (but not statistically significant) protective effect on mortality or viral clearance compared to the macrolide-free approach [145]. In a clinical trial carried out in 40 children with RSV infection randomized between AZM (10 mg/kg once a day for 7 days, then 5 mg/kg once a day for an additional 7 days) and placebo treatment for 14 days showed a significant statistical reduction in IL-8 and wheezing were put forward in the AZM group compared to placebo. An anti-inflammatory effect has been advanced to explain the decrease in the release of cytokines [146]. In another clinical trial on 50 patients hospitalized for influenza, randomized between oseltamivir versus oseltamivir and AZM, the effect on viral clearance was not significant, on the other hand, the decrease in pro-inflammatory cytokines (IL-6, IL-18, IL-17, CXCL-8, CXCL-9, sTNFR-1) and C-reactive protein was faster in the group receiving AZM and oseltamivir compared to the oseltamivir alone [13]. AZM increases the pH of organelles such as trans-Golgi network and endosome in primary bronchial epithelial cells and then alters the intracellular activities of virus [147]. These organelles play a significant role in packaging the proteins into vesicles for secretion, in a process exploited by the viruses to facilitate their replication [147]. The increase in pH of these organelles may alter the glycosylation of ACE2 (Angiotensin-Converting Enzyme 2) and therefore inhibit SARS-CoV-2 and host-cell interaction [147]. AZM reduces the level of furin in the spike protein of SARS-CoV-2, and therefore prevents the viral entry into the cells (Fig. 1) [147].

In summary, several *in vitro* studies showed a possible antiviral and anti-inflammatory effect of CQ/HCQ and AZM in preclinical models of viral infections. Different hypotheses on the mechanism of antiviral and anti-inflammatory activities have been proposed. CQ or its derivative HCQ and AZM have been used in treating COVID-19 patients [4,125,

131]. *In vitro* evaluation indicated that HCQ and AZM exhibit a synergistic effect on SARS-CoV-2 at concentrations similar to that achieved in humans [148]. Additionally, AZM increases the effectiveness of HCQ in decreasing the viral load [149]. Several studies published at the start of the COVID-19 pandemic have confirmed the effectiveness of CQ on COVID-19. An *in vitro* study conducted in China demonstrated that CQ prevents the entry steps as well as the release of SARS-CoV-2, thus preventing its replication and propagation in the host [150]. Another study reported an apparent efficacy and an acceptable tolerance of a treatment based on CQ in view of the data from 10 hospitals in Guangzhou, Shanghai, Beijing, Jingzhou, Chongqing, Wuhan, and Ningbo in China [125]. HCQ also presented encouraging results in clinical studies showing the high rates of patients' recovery in comparison to the untreated COVID-19 patients in France, China, and Italy [18,151–155]. Despite the small number of patients (i.e., sample size), these studies show that these drugs deserve deeper investigations. It was also shown in several studies that the association of HCQ with AZM increases the treatment effectiveness in comparison to HCQ alone [18, 153,152–155].

Besides the studies showing the effectiveness of HCQ associated with AZM, some studies revealed adverse effects, which limit the administration of this treatment to COVID-19 patients [156–158]. These adverse effects include prolonged QT interval, death, and transfer to intensive care with the persistence of virus after 6 days of treatment in more than 80 % of the patients [159,160]. Moreover, an RCT (ChiCTR2000029868) revealed no significant difference in the rate of viral elimination between HCQ and standard of care [160]. A retrospective study on 807 COVID-19 patients in the USA concluded that HCQ used alone or in combination with AZM did not reduce the risk of mechanical ventilation but increased the mortality [161]. In another retrospective study conducted in the USA on 1376 patients showed that HCQ does not reduce or increase the risk of a composite endpoint for intubation or death [162]. In a randomized trial (NCT04308668) of HCQ as the post-exposure prophylaxis for COVID-19 conducted across the USA and Canada, HCQ did not show significant results between the participants receiving HCQ (49/414) and those receiving placebo (58/407) [163]. In this study, no significant adverse effects were reported in the HCQ group. Moreover, an early administration of HCQ did not reduce the severity of symptoms in non-hospitalized patients with early COVID-19 in another randomized trial (NCT04308668) [164]. In Spain, an early administration of HCQ to mild COVID-19 patients did not improve the viral clearance, disease regression, and symptoms reduction. In this study, the HCQ-treated patients experienced adverse events during the 28 days of follow up [165]. In another RCT (NCT04381936) conducted in 176 hospitals across the United Kingdom on 7,513 participants, HCQ did not reduce the mortality rate after 28 days compared to the standard of care. Moreover, the patients who received HCQ had a longer hospital stay associated with a higher risk of undergoing mechanical ventilation [166]. Additionally, HCQ provided no clinical benefit in 11,000 hospitalized patients with COVID-19 in phase 2/3 clinical trials (NCT04381936) across the United Kingdom [167]. Among the 504 COVID-19 hospitalized patients, HCQ, as well as HCQ/AZM regiments, did not improve the clinical outcomes after 15 days in an RCT (NCT04322123) performed in Brazil. In this study, patients treated with HCQ/AZM (39.3 %) or HCQ alone (33.7 %) presented adverse events, whereas the standard of care group showed 22.6 % of adverse outcomes [168]. In another RCT (NCT04321278) conducted in 57 centers in Brazil, the patients treated with AZM/HCQ presented adverse events with no special improvement regarding healing [169]. Similarly, The European discovery trial (NCT04315948) and the World Health Organization (WHO)/Solidarity trial have stopped their clinical trials, declaring that the CQ/HCQ did not reduce the death rate in hospitalized COVID-19 patients compared to the standard care [170,171]. Based on scientific data associated with serious adverse effects, the US Food and Drug Administration (US FDA) revoked the authorization for emergency use of CQ and HCQ, stating that these two drugs are not effective in treating COVID-19 [172]. Similarly, the US National Institutes of Health (NIH), Agenzia Italiana del Farmaco (AIFA), European Medicines Agency (EMA), and Infectious Disease Society of America (IDSA) did not recommend the use of CQ/HCQ or CQ/HCQ/AZM for COVID-19 treatment in hospitalized and non-hospitalized patients [173–175]. Among the adverse effects associated with CQ/HCQ and AZM, the QT prolongation was the most common [176–178]. It was recorded in several countries on COVID-19 patients treated with HCQ/AZM combination with prolongations exceeding 500 ms in some studies [158,176]. The rate of HCQ/AZM treated patients presenting QT prolongation ranges from 0.77 % to 61 %, according to some studies [158,176,179]. The polymorphic ventricular tachycardia or fibrillation, acute kidney failure, and resuscitated cardiac arrest were also recorded in the patients under HCQ/AZM treatment [169,177]. In a randomized, double-blind, and phase 2b study (NCT04323527), a high dose of CQ (600 mg x 2/day for 10 days) was associated with an increased risk of the prolonged QT interval and mortality in severe COVID-19 patients, mainly when used in combination with AZM compared to low dose (450 mg x 2/1day followed by 450 mg x 1/day for 4 days) [180]. A reduced dose of CQ/HCQ results in a normal QT interval [178].

Overall, elevated doses of CQ/HCQ or their combination with AZM are associated with serious adverse effects and do not provide post-exposure prophylaxis nor reduce the infection rate. However, at this time, no significant antiviral results regarding the impacts of CQ/HCQ on the first viral phase of COVID-19 have been reported. In contrast, the inhibition of IFNs production, an essential pivot of host defense against SARS-CoV-2, by CQ/HCQ may exclude the use of the latter in the viral phase of COVID-19. Besides, CQ/HCQ administration may not control the entire inflammatory process (i.e., cytokine storm) in the COVID-19 course compared to other anti-inflammatory drugs [181,182].

4. Vaccine for coronaviruses

Effective SARS-CoV-2 vaccines are required to control the COVID-19 pandemic [183]. Presently, no vaccine is approved to prevent the SARS-CoV-2 infection. It was shown that coronavirus S protein, that binds to ACE2 during the infection process, is highly conserved between SARS-CoV-2, SARS-CoV, and MERS-CoV, indicating this protein a good vaccination target [184]. It was shown that SARS-CoV-2 infection induces the production of protective antibodies [185]. Two monkeys were protected from re-infection during the convalescence period after recovering from SARS-CoV-2 infection [186]. In a study carried out in Shanghai on 175 COVID-19 patients, 30 % showed a low titer of neutralizing antibodies (NAbs), whereas undetectable titers were registered in 10 patients [187]. These results demonstrate that a robust antibody response necessary for lasting the immunity is not systematically induced by mild COVID-19. Epidemiological analyses have projected that infections with other coronaviruses causing mild cold symptoms only confer immunity for approximately one year [188]. The NAb titers decreased 2–3 years post-infection in individuals infected with SARS-CoV or MERS-CoV [189,190], indicating that immunity may not last a lifetime even with more serious coronaviral infections. Sub-neutralizing or non-NAbs against certain epitopes of SARS-CoV may induce the Antibody Disease Enhancement (ADE), which results in negating the main objective of vaccination. These antibodies can improve the entry of the virus into the human cells either by interacting with the conformational epitopes in the ACE2-binding domain [191] or *via* the Fcγ II receptor [192]. Although the *in vivo* significance of these results remains to be determined, we can add the ADE to the list of concerns that need to be addressed in the COVID-19 vaccine development. Three methods have been proposed to alleviate the harmful effects of ADE, including the shielding of the non-neutralizing epitopes of the S proteins, immunofocusing marking only the critical neutralizing epitope, and removing the epitope sequences which promote the ADE [193,194]. The protein sequences responsible for ADE have been recognized at $S_{597\text{-}603}$ of the SARS-CoV S protein, a section that is also

preserved in SARS-CoV-2. Therefore, the COVID-19 vaccines could be developed to decrease the ADE *via* the removal of the epitope [193,194]. It was shown that the COVID-19 vaccine comprising residues of S-$RBD_{319-545}$ (S-Receptor-Binding Domain) induce a strong protective antibody immune response in non-human primates, rabbits, and mice [185]. ADE is of clinical impact in some viral infections, including MERS-CoV, SARS-CoV [195,196], influenza [197], Dengue virus [198,199], RSV [200], HIV [201,202], and Ebola virus (EBV) [197,203]. The vaccine PiCoVacc Sinovac Biotech candidate was administered to non-human primates, rats, and mice [204], where the immune system induced in animals was able to combat SARS-CoV-2 strains without observable ADE of infection. Similarly, partial or whole protection in animals against SARS-CoV-2 was achieved after three immunizations of two doses (3 μg or 6 μg per dose) each. Recently, Chinese macaques infected with SARS-CoV after being vaccinated with a modified vaccinia virus Ankara (MVA) coding for the glycoprotein SARS-CoV S produced a high titer of antibodies associated with reduced viral load [205]. However, these macaques showed severe acute lung damage associated with diffuse alveolar damage. Immunization of mice with an inactivated SARS-CoV with or without adjuvant or a recombinant baculovirus expressing an S protein or particles of coronavirus (VLP) reduced the occurrence of morbidity and mortality related to the virus by decreasing the viral load [206,207]. However, histopathological findings revealed the type 2 inflammatory response at the pulmonary level characterized by the eosinophilic pulmonary infiltrates. The vaccine against the RSV [208] and recombinant vaccinia virus (VV) [209] expressing the SARS-CoV S and N proteins have also shown pneumonia or pulmonary manifestations in pediatric subjects and mice, respectively. Similarly, the inactive MERS-CoV vaccine candidate has also induced NAbs in mice associated with type 2 pulmonary pathology as depicted by the eosinophilic infiltration and elevated concentrations of IL-13 and IL-5 [210]. Interestingly, TLR agonists [211] or Inulin Delta [212] could be used as an adjuvant to improve the healing of type 2 lung disease. An immunization study involving ferrets, naturally susceptible to SARS-CoV, revealed that the recombinant vaccinia virus Ankara (rMVA) expressing the SARS-CoV S induces a rapid and high titer of NAbs. However, the rMVA-S immunized ferrets developed severe hepatitis [213]. Several attempts to develop vaccines against the coronavirus (FIPV) which causes feline infectious peritonitis (FIP) in cats have failed. In fact, the vaccination induced low levels of NAbs, and the immune response induced by the FIPV vaccine was turned out harmful to the animals [214,215]. When the FIPV virus was injected into animals, the mortality of the treated group was further elevated compared to the control group [214]. The hypothesis was that the virus itself, in the presence of antibodies and macrophages, induced the formation of immune complexes that led to the mortality in immunized animals [216]. These data, on previous vaccine experiments with coronaviruses, suggest that the histopathological pulmonary and clinical evaluation should be carried out during the preclinical development of SARS-Cov2 vaccines.

The vaccine approach often chosen is the induction of antibody-based immunity [217]. Unfortunately, the immune system cannot be reduced to antibody-based immunity alone but works in a coordinated and complementary manner, especially concerning the antiviral immunity [218]. Furthermore, the main difficulty in implementing a candidate vaccine against the viral infections is the ability of a vaccine to produce a high level of NAbs, hence the importance of acting on innate immunity, then on cell-mediated immunity as a vaccine supplement. Additionally, the problem of setting up a good design comes mainly from the extreme genetic variability of viruses. HIV is the perfect example, where during the progression of natural infection, only 1% of the individuals produced NAbs which can neutralize most HIV-1 subtypes [219,220]. Genetic analyses of 86 SARS-CoV-2 genomes have provided evidence of genetic diversity by revealing numerous mutations and deletions on coding and non-coding regions [221]. A study reported that 198 sites in the SARS-CoV-2 genome seem to have already undergone mutations [222], but the genetic variability of SARS-CoV remains limited compared to other RNA viruses such as HIV [223]. SARS-CoV-2 displays, like other RNA viruses, a relatively high potential of mutation that can cause the evolution of potential epitopes. Additionally, a mutation in SARS-CoV-2 spike protein such as D614 G may increase its infectivity and make the vaccine less effective [224]. In parallel, the B cells, which produce antibodies, are also subject to the phenomena of somatic mutations at the origin of antibody variants exhibiting increasingly optimized activities [225]. There is, therefore, competition between the immune system and the virus. Thus, after several years of infection, this phenomenon of optimization of recognition sometimes leads to the appearance of more active antibodies capable of accessing very conserved areas of the virus [225]. This results in a broad-spectrum neutralization capacity, effective against many viral isolates; called broadly NAbs, or bNAbs.

Numerous COVID-19 vaccine technologies are in the process of development, including the DNA, RNA, protein subunit, live attenuated virus, inactivated virus, virus-like particles, non-replicating, and replicating viral vectors vaccines [226]. To date, 201 COVID-19 candidate vaccines have been listed by WHO landscape summary, out of which 45 are under clinical evaluation, including 21 in phase 1 (safety and dosage evaluation), 12 in phase 1/2, 2 in phase 2 (safety, immunogenicity and immunization process evaluation), 1 in phase 2/3, and 9 in phase 3 (safety and effectiveness evaluation) clinical trials (Table 2) and 156 in preclinical evaluation (efficacy and safety) [226]. A preliminary report of phase 1 clinical trial (NCT04283461) showed that candidate vaccine mRNA-1273 induced an immune response in 45 healthy participants (18–55 years old) with elevated levels of antibodies against the SARS-CoV-2 on day 28 without significant local or systemic adverse events [227]. The induction of antibodies was dose-dependent, and the titers of NAbs increased after the second vaccination. Moreover, this candidate vaccine induced T cells response with more T helper (Th) 1 cytokine (IFN-γ, TNF-α, IL-2) than the Th2 (IL-4, IL-13). The Th1 cell is often involved in antiviral immune responses by inducing the cell-mediated immunity, while the primary role of Th2 is to initiate an antibody response cooperating with B cell [228]. The Th1/Th2 cytokine profile constitutes an essential basis for the development of viral vaccines [228]. In the final study comprised of 40 aged adults ($\geq$ 56 years old), the vaccine mRNA-1273 induced the NAbs and T cell immune response [229]. The side effects such as headache, pain at injection, chills, and myalgia were dose-dependent and increased after the second vaccination. In phase 1/2 clinical trial (NCT04324606), the ChAdOx1-S candidate vaccine induced a strong antibodies response in 1077 participants on day 28 and cellular immune response on day 14 [230]. All participants showed production of higher NAbs after receiving a second dose of the vaccine. The side effects such as headache, malaise, fever, chills, muscle ache, and pain were reduced by administering the prophylactic paracetamol to participants. Similarly, the Ad5 vectored COVID-19 candidate vaccine induced a robust NAbs response at day 28 and specific T cellular response at day 14 in most of the 108 participants included in the phase 1 clinical trial (NCT04313127) [231]. The side effects were associated with a higher dose of vaccine. In the phase 2 trial (NCT04341389), the Ad5 vectored COVID-19 candidate vaccine induced a strong immune response in the majority of 508 participants without side effects [232]. Moreover, the COVID-19 RNA vaccine BNT162b1 in phase 1/2 (NCT04368728) induced a strong NAbs in 45 participants. The NAbs titers were significantly higher than those of a panel of COVID-19 convalescent human plasma [233]. Most participants developed a Th1 response associated with IFN-γ production without severe adverse events. The robust NAbs associated with favorable IFN response is beneficial for protection against COVID-19 [234]. In two RCTs comprised of 96 adults in phase 1 and 224 adults in phase 2 (ChiCTR2000031809), the interim analysis of the inactivated vaccine against SARS-CoV-2 from Wuhan Institute of Biological Products/Sinopharm reported that the vaccine induced a NAbs response in all participants after 14 days without severe adverse reactions [235]. The NAbs increased significantly after the second and third immunization

Table 2
Vaccines under clinical evaluation for COVID-19 according to the WHO as of October 29, 2020. The information provided here are based on the analysis from official website of WHO [226].

Platform	Candidate vaccine (Developer)	Current stage (participants)	Status (completion date)	Subject	Study location
Inactivated	Inactivated + alum (Sinovac)	Phase 3 NCT04456595 (8,870)	Recruiting (October 2021)	18−59 years	Brazil
		Phase 1/2 NCT04383574 (422)	Recruiting (December 2020)	18−59 years	China
		NCT04352608 (744)			
	Inactivated (Wuhan Institute of Biological Products/Sinopharm)	Phase 3 ChiCTR2000034780 (15,000)	Recruiting (July 2021)	≥18 years	United Arab Emirates
		Phase 1/2 ChiCTR2000031809 809 (1,120)	Completed	18−59 years	China
	Inactivated (Beijing Institute of Biological Products/Sinopharm)	Phase 3 ChiCTR2000034780 (15,000)	Recruiting (July 2021)	≥ 18 years	China
		Phase 1/2 ChiCTR2000032 459 (1,904)	Recruiting (-)	≥ 3 years	China
	Inactivated (Research Institute for Biological Safety Problems, Rep of Kazakhstan	Phase 1/2 NCT04530357 (244)	Recruiting (April 2021)	18−100 years	Kazakhstan
	Inactivated (Beijing M Inhai Biotechnology Co., Ltd.,)	Phase 1 ChiCTR2000038804 (180)	Not yet recruiting (-)	≥ 18 years	China
	Inactivated (Institute of Medical Biology Chinese Academy of Medical Sciences)	Phase 1/2 NCT04412538 (942)	Recruiting (September 2021)	18−59 years	China
		NCT04470609 (471)	(November 2021)	≥ 60 years	China
	Whole-Virion inactivated (Bharat Biotech)	Phase 1/2 NCT04471519 (755)	Active, not recruit ing (June 2021)	12−65 years	India
	ChAdOx1-S (University of Oxford/ Astrazeneca)	Phase 3 ISRCTN8995424 (2000)	Recruiting (July 2021)	18−55 years ≥ 18 years	Brazil
		Phase 2b/3 2020-001228-32 (-)	Recruiting (-)	18−65 years with or wit hout HIV	UK South Africa
		Phase 1/2 PACTR20200692216 5132 (2000)	Recruiting (December 2021)		UK
		NCT04324606 (1090)	Completed	18−55 years	
	Adenovirus Type 5 Vector (Cansino Biological Inc./Beijing Institute of Biotechnology)	Phase 3 NCT04526990 (40,000)	Recruiting (January 2022)	≥ 18 years	Pakistan
		Phase 2 ChiCTR2000031781 (500)	Completed	≥ 18 years	China
		Phase 1 ChiCTR2000030906 (108)	Completed	18−60 years	China
Non-replicating viral	Replication defective Simian Adenovirus (GRAd) encoding S (ReiThera/LEUKOCA RE/Univercells)	Phase 1 NCT04528641 (90)	Recruiting (July 2021)	18−85 years	Italy
	Ad5-nCoV(Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China	Phase 1 NCT04552366 (144)	Recruiting (June 2021)	≥ 18 years	China
	Adeno-based (Gamaleya Research institute)	Phase 3 NCT04530396 (40,000)	Recruiting (May 2021)	≥ 18 years	Russia
		Phase 1/2 NCT04436471 NCT04437875 (38)	Active, not recruit ing (August 2020)	18−60 years	Russia
	Ad26COVS1(Janssen Pharmaceutical Companies)	Phase 3 NCT04505722 (60,000)	Recruiting (March 2023)	≥ 18 years	USA, Peru Argentina Brazil, Chile Mexico, South Africa, Columbia
		Phase 1/2 NCT04436276 (1045)	Recruiting (November 2023)	≥ 18 years	USA Belgium

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Table 2 (*continued*)

Platform	Candidate vaccine (Developer)	Current stage (participants)	Status (completion date)	Subject	Study location
	Ad5 adjuvanted Oral Vaccine platform (Vaxart)	Phase 1 NCT04563702 (48)	Recruiting (October 2021)	18−54 years	USA
	MVA-SARS-2-S (Ludwing-Maximillians- -University of Munich)	Phase1 NCT04569383 (30)	Not yet recruiting (May 2021)	18−55 years	Germany
	LNP-encapsulated mR NA (Moderna/ NIAID)	Phase 3 NCT04470427 (30,000)	Recruiting (October 2022)	≥ 18 years	USA
		Phase 2 NCT04405076 (600)	Active, not recruit ing (August 2021)	≥ 18 years	USA
		Phase 1 NCT04283461 (155)	Completed	18−99 years	USA
	3LNP-mRNAs (BioNTech/Fosun Pharma/Pfizer)	Phase 2/3 NCT04368728 (43,998)	Recruiting (November 2022)	18−85 Years	USA Argentina Brazil
		Phase 1/2 2020-001038-36 (444)	Recruiting (-)	≥ 18 years	Germany
RNA		Phase 1 ChiCTR2000034825 (144)	Recruiting (December 2020)	≥ 18 years	China
	LNP-nCoVsaRNA (Imperial College London)	Phase 1 ISRCTN17072692 (320)	Recruiting (July 2021)	18−75 years	UK
	mRNA (Curevac)	Phase 2 NCT04515 147 (691)	Not yet recruiting (November 2021)	≥ 18 years	Germany Belgium
		Phase 1 NCT04449276 (168)	Recruiting (August 2021)	18−60 years	Germany Belgium
	mRNA (People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech)	Phase 1 ChiCTR2000034112 (168)	Not yet recruiting (December 2021)	18−80 years	China
	mRNA(Arcturus/Duke -Nus)	Phase 1/2 NCT04480957 (92)	Recruiting (January 2021)	21−80 years	Singapore
	DNA plasmid vaccine with electroporation (Inovio Pharmaceuticals/International Vaccine Institute)	Phase 1/2 NCT04447781(160)	Recruiting (February 2022)	19−64 Years	Republic of Korea
		Phase 1 NCT04336410 (120)	Recruting (July 2021)	≥ 18 years	USA
DNA	DNA plasmid + Adjuvant (Osaka University/AnGes/TakaraBio)	Phase 1/2 NCT04463472 (30)	Recruiting (July 2021)	20−55 years	Japan
	DNA plasmid vaccine (Cadila Healthcare Limited)	Phase 1/2 CTRI/2020/07/0 263552 (1048)	Recruiting (July 2021)	18−55 years	India
	DNAVaccine (GX-19) (Genexine Consortium)	Phase 1 NCT04445389 (210)	Recruiting (June 2022)	18−50 years	Republic of Korea
Protein Subunit	Full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M (Novavax)	Phase 3 (2020-004123-16)	Recruiting (-)	≥ 18 years	UK
		(-)	Recruiting (November 2021)	18−64 Years	South Africa
		Phase 2b NCT04533399 (2,900)	Recruiting (July 2021)	18−59 years	USA
		Phase 1/2 NCT04368988 (131)			
	Native-like Trimeric subunit spike protein vaccine (Clover Bioph Pharmaceuticals Inc. /GSK/Dynavax)	Phase 1 NCT0440590 (150)	Recruiting (March 2021)	18−75 years	Australia
	RBD (Baculovirus production expressed in Sf9 cells) (West China Hospital, Sichuan University	Phase 1 ChiCTR2000037518 (168)	Recruiting (August 2021)	≥ 18 years	China
	Adjuvanted recombinat protein (RBD Di mer) (Anhui Zhifei Longcom Biopharmaceutical /Institute of Microbiology , Chinese Academy of Sciences)	Phase 2 NCT04466085 (900)	Recruiting (December 2021)	18−59 Years	China
		Phase 1 NCT04445194 (50)	Recruiting (September 2021)	18−59 years	China
	S protein (Baculovirus Production) Sanofi Pasteur/GSK	Phase 1/2 NCT04537208 (440)	Recruiting (October 2021)	≥ 18 years	USA
	Recombinant spike protein with Advax™	Phase 1 NCT04453852 (40)	Recruiting (July 2021)	18−65 years	Australia

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Table 2 (*continued*)

Platform	Candidate vaccine (Developer)	Current stage (participants)	Status (completion date)	Subject	Study location
	Adjuvant (Vaxine Pty Ltd./Medytox)				
	SARS-CoV-2 HLA-DR peptides (University Hospital Tuebingen)	Phase 1 NCT04546841 (36)	Not yet recruiting (December 2021)	≥ 18 years	Germany
	Molecular clamp stabilized spike protein (University of Queensland /GSK/Dynavax)	Phase 1 ACTRN1262000067 4932P (120)	Recruiting (-)	18−55 years	Australia
	RBD-based (Kentucky Bioprocessing, Inc)	Phase 1/2 NCT04473690 (180)	Not yet recruiting (November 2021)	18−70 years	USA
	S1-RBD-protein (COVAXX)	Phase 1 NCT04545749 (60)	Recruiting (August 2021)	20−55 years	Taiwan
	S-2 P protein + CpG101 8(Medigen Vaccine Biologics corporation/NIAID /Dynavax	Phase 1 NCT04487210 (45)	Not yet recruiting (December 2021)	20−50 years	Taiwan
	RBD + Adjuvant (Instituto Finaly de Vacunas, Cuba	Phase 1/2 IFV/COR/04 (676)	Recruiting (Febuary 2021)	19−80 years	Cuba
	Peptide (FBRI SRC VB B VECTOR, Rospotrebnadzor , Koltsovo)	Phase 1/2 NCT04527575 (100)	Active, not recruit Ing (October 2020)	18−60 Years	Russia
VLP	Plant-derived VLP (Medicago Inc. ./Universite' Lava)	Phase 1 NCT04450004 (180)	Recruiting (April 2021)	18−55 years	Canada
	RBD-HBsAg VLPs (SpyBiotech/serum Institute of India	Phase 1/2 ACTRN126200000 817943 (280)	Recruiting (-)	18−79 years	Australia
Replicating viral vector	Intranasal flu-based-RBD (Beijing Wantai Biological Pharmacy/ Xiamen University	Phase 1 ChiCTR2000037782 (60)	Not yet recruiting (October 2021)	≥ 18 years	China
	Meascles-vector based (Institute Pasteur/Thermis/University of Pittsburg CVR/Merck Sharp & Dohme)	Phase 1 NCT04497298 (90)	Recruiting (October 2021)	18−55 years	France Belgium

suggesting the necessity for at least two immunizations. Furthermore, analysis from two open and non-randomized phase 1/2 (NCT04436471/NCT04437875) trials showed that the rAd26 and rAd5 vector-based vaccine induced a strong NAbs at day 14 and cell-mediated immunity with favorable median CD4+ and CD8 + T cells proliferation associated with IFN-γ production at day 28 in 76 participants. The minor adverse events such as asthenia (21 %), headache (42 %), hyperthermia (50 %), and pain at the injection site (24 %) were reported [236]. In this trial, participants who received the vaccine had the same titer of NAbs against SARS-CoV-2 as recovering COVID-19 patients suggesting a capability of natural SARS-CoV-2 infection to induce NAbs. In phase 1/2 trial (NCT04368988), 83 healthy participants received the rSARS-CoV-2 vaccine with adjuvant (Matrix-M), 25 without Matrix-M, and 23 healthy participants received placebo [237]. The rSARS-CoV-2 vaccine adjuvanted with Matrix M1 (NVX-CoV2373) induced strong antibody and Th1 immune response compared to the vaccine without adjuvant. The titers of NAbs induced by the adjuvanted dose was significantly higher than those of convalescent human plasma. More Th1 cytokines (IFN-γ, TNF-α, IL-2) were induced than Th2 (IL-5, IL-13), suggesting the importance of cell-mediated immunity in viral clearance. All participants reported no severe adverse events. At this stage of clinical trials, the direct comparisons between different candidate vaccines should be interpreted with caution due to the small size of the trials, the different doses of vaccine used, and the variety of analytical methods.

Overall, most of the COVID-19 vaccines with the published report have induced the production of NAbs and T cell immune response after the activation of SARS-CoV-2-specific $CD4^+$ and CD8 + T cells. The CD4 + T cell is at the center of the initiation of the adaptive immune response, which can be either an antibody immune response or a cellular response or both responses depending on the type of pathogen [238]. The production of antibodies is an essential part of the immune response following the infection or vaccination. The antibodies are produced by the B cells and are specific for the antigens that trigger the immune response. The term neutralization relates to the formation of the immune complex which prevents the biological activity of the antigen [239]. This neutralization function is the main correlate of protection of many vaccines and convalescent plasma. The antibodies are also able to interact with many cells of the immune system through the receptors which recognize the constant region of immunoglobulins called the fragment crystallizable (Fc). These Fc receptors (FcR) are necessary for the proper functioning of the humoral response, for example for the clearance of immune complexes. Different types of cells of the immune system express these FcRs, allowing the induction of effector functions complementary to neutralization [240]. Among these, the antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADP) target the cells or the antigenic elements that have been recognized and are covered by antibodies and lead to their destruction (Fig. 5) [240]. The cellular effectors of ADCC are mainly NK (natural killer) cells, which express the CD16 molecule (or FcγRIII), an FcR that recognizes the isotype G immunoglobulin. Moreover, monocytes, neutrophils, and macrophages are also involved in ADCC.

The CD8 + T cells are involved in the adaptive cell-mediated immune response, which is an effective immune response against viruses and other intracellular parasites [241]. The effective control of viral infection requires the elimination of the infected cells in order to limit the production and the propagation of the virus as well as the establishment of an immune memory specifically directed against the viral antigens. The latter relies on the expansion of cytotoxic CD8 + T lymphocytes (CTL) [242]. In SARS-CoV survivors, the CD8 + T cells conferred lasting

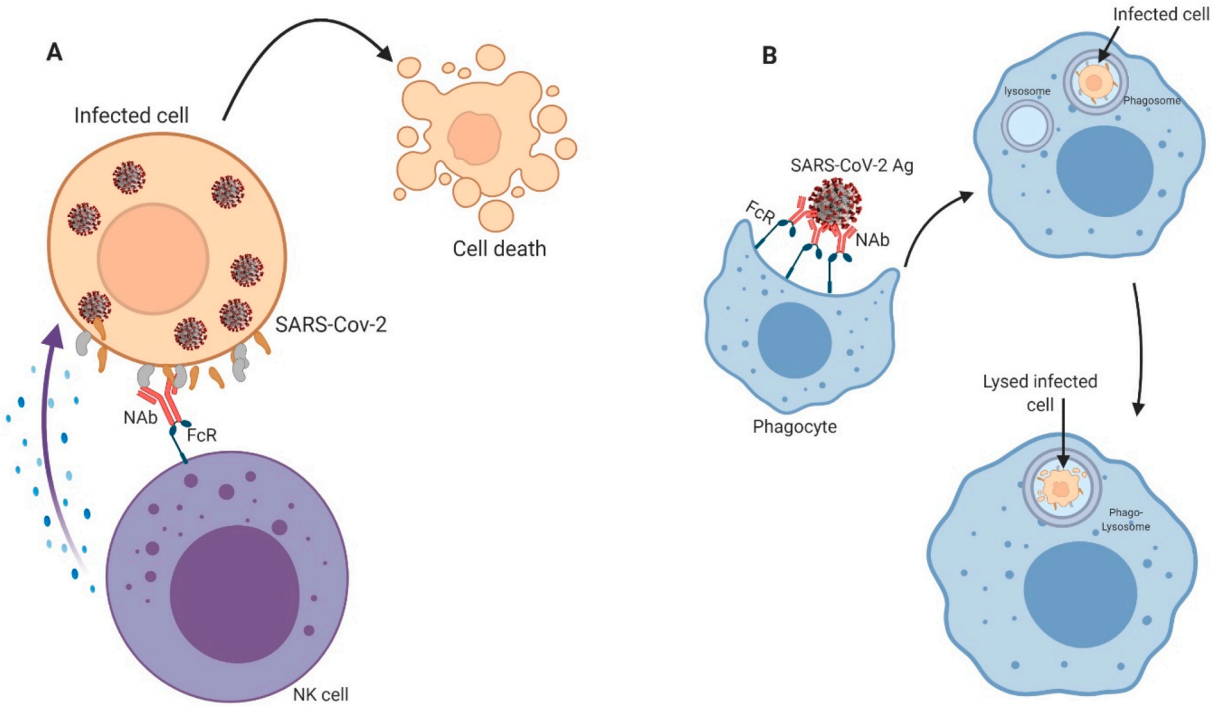

Fig. 5. Schematic representation of ADCC and ADP induced by neutralizing antibodies (NAbs). A cell infected with SARS-CoV-2 expresses viral antigens on its surface, that allows certain NAbs to attach to the plasma membrane. The NK (natural killer) cells (A) and phagocytes (B) are then activated *via* the receptor for the Fc fragment of immunoglobulins. The NK cells then release cytolytic granules (granzymes and perforins), and phagocytes internalize the virus-infected cell in the phagolysosome. Both cytolytic granules and phagolysosome destroy the infected cell recognized by the NAbs.
ADCC, antibody-dependent cellular cytotoxicity; ADP, antibody-dependent phagocytosis (ADP).

immune memory that persisted up to 11 years [243]. The candidate vaccine such as COVID-19 RNA vaccine BNT162b induced a robust release of IFN-γ, which participate in several antiviral responses in particular by inhibiting the replication of SARS-COV-2. The robust CD8+ producing IFN-γ with antiviral properties could complement the strong response of NAbs. Furthermore, the SARS-COV-2 specific cellular immune response could be effective in controlling the COVID-19, even in the absence of NAbs [244]. Therefore, the vaccine inducing strong NAbs and cell-mediated immune response could be effective in controlling the COVID-19 pandemic.

The BCG (Bacillus Calmette–Guérin) is an example of a vaccine that induces innate immunity [245]. It is a live vaccine obtained from the attenuation of *Mycobacterium bovis* strain that is injected into the infants usually in the first year after their birth [245]. The BCG vaccine has other long-standing effects, including the protection against other types of respiratory infections such as RSV infection [246–248]. BCG, as a live vaccine, induces the expression of genes which are involved in the innate immunity (trained immunity) as well as long-term cellular immunity [249,250]. The BCG vaccine offers protection up to 60 years of immunization, and therefore the old population must be revaccinated [249]. This very broad spectrum immunity presents a form of memory which would somehow be boosted by these live vaccines since they are real pathogens, even weakened. This practice would help the body to better regulate its overall immune response [250]. COVID-19, in the last phase of the infection, disrupts the inflammatory system (cytokine storm), which ends up in catastrophic chain reactions in the patient [5,6]. However, the aforementioned trained innate immunity would prevent such unwanted chain reactions, and therefore partly avoid the severe cases of the disease. A recent publication shows that the nationwide differences in the impact of COVID-19 could be explained, in part, by the national policies concerning the vaccination of children with BCG [251]. Thus, countries without a BCG vaccination policy (United States, Italy, the Netherlands) were more seriously affected than those with long-standing universal BCG policies. In European countries, each 10 % increase in the BCG index was associated with a 10.4 % drop in the mortality from COVID-19 [252]. Clinical trials are underway in the Netherlands (NCT04328441) [253], South Africa (NCT04379336) [254], and Australia (NCT04327206) [255] to confirm this association.

5. Concluding remarks

More effective COVID-19 patient management protocols to ensure the reduced need for prolonged mechanical ventilation, short hospital stays, and to reduce the morbidity and mortality associated with COVID-19 are still lacking. Despite the controversial results of CQ/HCQ and AZM in the treatment of COVID-19 in recent days, several countries continue to allow their use in the treatment of COVID-19 patients. However, the use of CQ/HCQ and AZM should remain restrained because the results of new studies do not validate these treatments in the management of COVID-19. Nevertheless, in the situation of a supposed bacterial super-infection that can complicate the COVID-19, clinicians may wish to prescribe AZM. The lung injury in COVID-19 patients is associated with ROS release by phagocytes, and thus the use of antioxidants is necessary for the management of COVID-19. Besides, type I and type III IFNs have shown antiviral activities both in *vitro* and *in vivo*. Type I IFN was effective in treating COVID-19 patients than other forms of treatment without IFN; thus, we hypothesize that the use of type I and III IFNs in the early stage of COVID-19 combined with an adapted antioxidant and anti-inflammatory drug in the advanced stage could help improve the clinical outcomes. The vaccine remains an efficient agent for COVID-19 protection, and the preliminary reports of the candidate vaccines showcase some encouraging results.

Author contribution

The manuscript was written through the contribution of all authors.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest associated with the publication of this manuscript.

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