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Review

Chemotherapy vs. Immunotherapy in combating nCOVID19: An update

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ABSTRACT

The nCOVID-19 pandemic initiated its course of contagion from the city of Wuhan and now it has spread all over the globe. SARS-CoV-2 is the causative virus and the infection as well as its symptoms are distributed across the multi-organ perimeters. Interactions between the host and virus governs the induction of 'cytokine storm' resulting various immunopathological consequences leading to death. Till now it has caused tens of millions of casualties and yet no credible cure has emerged to vision. This article presents a comprehensive overview on the two most promising remedial approaches that are being attempted for the management, treatment, and plausible cure of nCOVID-19. In this context, chemotherapeutic approach primarily aims to interrupt the interactions between the host and the virus causing inhibition of its entry into the host cell and/or its proliferation and suppressing the inflammatory milieu in the infected patients. On the other side, immunotherapeutic approaches aim to modulate the host immunity by fine tuning the inflammatory signaling cascades to achieve phylaxis from the virus and restoring immune-homeostasis. Considering most of the path-breaking findings, combinatorial therapy involving of chemotherapeutics as well as vaccine could usher to be a hope for all of us to eradicate the crisis

Contents

Abbreviations: COVID19, Coronavirus disease; SARS, Severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; RBD, Receptor-binding domain; TMPRSS2, Transmembrane protease, serine 2; ERGIC, ER-Golgi intermediate compartment; IL, Interleukin; TNF, Tumor necrosis factor; IFN, Interferon; ARDS, Acute respiratory distress syndrome; RT-PCR, Real-time fluorescence reverse-transcription polymerase chain reaction; CT, Computed tomography; WHO, World health organization; AZT, Azithromycin; ATP, Adenosine triphosphate; RCT, Randomized controlled trial; FDA, Federal drug administration; IMPDH, Inosine monophosphate dehydrogenase; RSV, Severe respiratory syncytial virus; CM, Camostat mesylate; GERD, Gastroesophageal reflux disease; HIV, Human immunodeficiency virus; LMWH, Low molecular weight heparin; SIC, Sepsis-induced coagulopathy; ARDS1, Acute respiratory distress syndrome1; PAMP, Pathogen associated molecular pattern molecules; GM-CSF, Granulocyte-macrophage colony-stimulating factor; JAK, Janus kinase; STAT, Signal transducers and activators of transcription; AAK1, AP2-associated protein kinase 1; IMQ, Imiquimod; BCG, Bacillus Calmette-Guerin vaccine; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; RdRp, RNA-dependent RNA polymerase; CSIR-IICT, Council of Scientific and Industrial Research's Indian Institute of Chemical Technology; IMPDH1, Inosine monophosphate dehydrogenase1; GOIMHRD, Government of India Ministry of Health & Family Welfare; GERD1, Gastroesophageal reflux disease1.

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1. Background

The coronavirus disease (COVID19) has already taken over 216 countries, has infected 126 million individuals and has taken away 2.77 million lives [1]. Almost the whole world has come to a standstill, it is the greatest crisis the mankind has faced since the Dark Ages. The disease exhibits a wide array of multi-organ malfunctioning symptoms [2] along with a range of magnitudes of expression from life-threatening to asymptomatic, depending upon the genetic predisposition and pathological vulnerability of the patient. Essentially, various strategies are being adopted to provide prophylaxis against the infection and also to treat the various conditions presented by the disease. The strategies can be broadly classified into two categories – chemotherapeutic and immunotherapeutic approaches. Chemotherapy involves administration of different drug molecules in order to alter the mechanism in which the infection expands, and finally retard its spread and also provide supportive care to the patients. The immunotherapy, however, uses specially designed immunogenic substances to either elicit or inhibit the immune system and thereby exploit it to counter the disease. The scientific research community and healthcare professionals from all over the globe are now focusing their research objectives towards one common goal – to find an absolute cure to this disease. This review is an attempt to learn the latest developments and to honor their contributions by exploring the varied approaches of treatment, from the ones that are currently being used to those which are yet in progressive research.

2. Chemotherapeutic interventions

At present no credible cure for nCOVID19 at sight the healthcare community has resorted to several chemotherapeutic strategies, aimed primarily at impeding the prognosis of the disease in the given subject. The approaches can be classified into various categories based upon their mechanism of action Figs. 1 and 2.

2.1. Anti-viral drugs

Anti-viral therapeutic drugs [3] mainly affect the initial infection phase of the virus contained primarily within the pulmonary sphere, and they do so by interacting with various components of the pathogenetic pathway of the SARS-CoV-2, like certain stages of adhesion, entry, endocytosis, protein cleavage, and its replication. Interfering with any of the given interactions produces retardatory effects on the viral infection Tables 1 and 2.

2.1.1. Chloroquine and hydroxychloroquine

Hydroxychloroquine and chloroquine have a broad history of being used in the treatment of diseases like malaria, SLE and RA. Recently they were brought forth by many of the early studies that were quested to find an immediate medication option to resist the SARS-CoV-2 infection in patients. A French study consisting of 36 subjects out of which 20 being in the hydroxychloroquine group and 16 in the control group, reported greater virologic clearance with 200 mg hydroxychloroquine when administered orally every 8 h, as compared with control subjects provided just with standard supportive care. Virologic clearance at day 6 which was measured by nasopharyngeal swabs, was 70% (14/20) vs 12.5% (2/16) for the hydroxychloroquine and control groups, respectively [4]. *In vitro* studies showed that when cells were treated with chloroquine the endosomal vesicles were abnormally enlarged. This indicated a modified maturation process of endosomes and blocking endocytosis, finally resulting in failure of further transport of virions to the

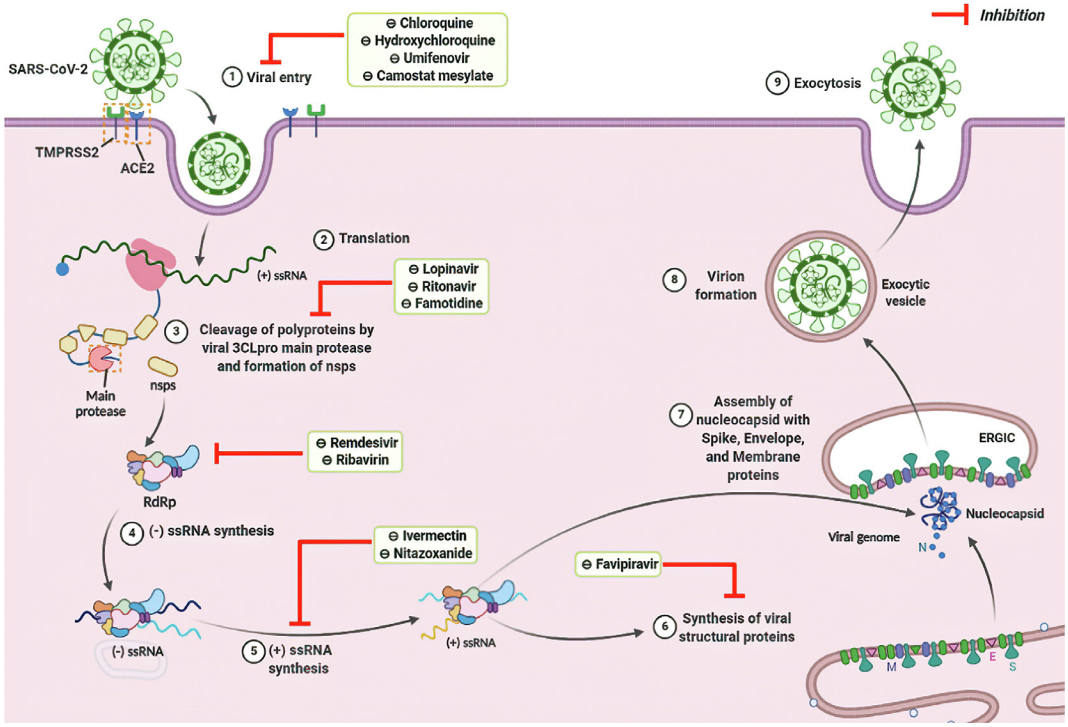

Fig. 1. Chemotherapeutic targets. The schematic simplifies the life cycle of the SARS-CoV-2 virus and the different mechanisms of action of the chemotherapeutic agents.

replication site. Hydroxychloroquine alters the membrane fusion and disrupts the budding process of mature virions. Moreover, they inhibit the viral entry into cells by inhibiting the glycosylation of host receptors and consequent proteolytic processing. They also seem to impair the correct recognition and maturation of viral antigens by antigen-presenting cells (APCs), which is why they are able to produce immunomodulation by attenuating the cytokine production and inhibiting the lysosomal activity and autophagy in host cells. The properties are clearly evident as hydroxychloroquine inhibits IL-1β, IL-6, and TNF-α release and it also exhibits anti-thrombotic properties that interfere with platelet aggregation and blood clotting proteins. Studies suggest that hydroxychloroquine promises a superior viral clearance when synergized with Azithromycin (AZT), a trail found viral clearance in 100% of the patients in combinatorial therapy, which is far superior to clearance in 57% patients yielded by hydroxychloroquine monotherapy [4]. Recent studies also suggest the possible effectiveness of formulations of hydroxychloroquine combined with fluoroquinolones. However, currently, hydroxychloroquine in combination with azithromycin is used mainly used for postexposure prophylaxis after high-risk exposures. The drugs are well tolerated and rarely produce any serious side effects like retinopathy, hypoglycemia, cardiovascular complications [5,6], and neuropsychiatric effects.

2.1.2. Remdesivir

Remdesivir, formally known as GS-5734, is a monophosphate prodrug and it undergoes metabolism to an active C-adenosine nucleoside triphosphate analogue. It has been shown to be highly effective against the Ebola virus [7] and now it promises to be a potential therapeutic option against the nCOVID19 as showed by its broad spectrum and potent *in vitro* activity against SARS-CoV, MERS-CoV as well as SARS-CoV-2 with EC_{50} value of 0.77 μM and a EC_{90} 1.76 μM [8]. The RdRp is a potent and critical drug target in resisting the SARS-CoV-2 infection cycle. However, targeting it shows low specificity and low potency, but Remdesivir is the best drug in the class available. Recent enzyme kinetics studies showed that RdRp efficiently incorporates the active triphosphate form of Remdesivir into RNA, while it outcompetes adenosine triphosphate (ATP) for the site, finally causing premature termination of the product RNA just after 3 more nucleotides are added to its chain [9]. According to a preliminary data analysis from a RCT that involved 1062 hospitalized patients (NCT04280705) with an advanced phase of nCOVID-19 with lung involvement, it showed that when were administered with Remdesivir they recovered faster than similar patients who received placebo. Currently, Remdesivir is not FDA-approved and is administered for compassionate purposes only.

2.1.3. Favipiravir

Favipiravir also is known as T-705, is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate. Supported by several studies, Favipiravir has been found to be effective against many viruses *viz.* Influenza virus, Ebola virus and arenavirus. Further, when used against SARS-CoV-2 *in vitro*, the EC_{50} of favipiravir was reported to be 61.88 μM/L in Vero E6 cells [10]. It acts as a purine nucleotide substrate for the RdRp and gets incorporated into the viral RNA strand preventing its further extension and ultimately inhibiting its activity leading to termination of viral protein synthesis. This mode of action combined with phylogenetic preservation of the catalytic domain in the RNA-dependent RNA polymerase enzyme across various RNA viruses, explains such a broad spectrum of activity of Favipiravir. Based on the type of indication different dosing regimens have been proposed. Dosage variations are most likely due to the higher Favipiravir EC_{50} values described against SARS-CoV-2 as compared with influenza, thus a dose at the higher end of the range is supposed to be considered for the treatment of nCOVID19. It is recommended to administer a loading dose of 2400 mg to 3000 mg every 12 h twice followed by a maintenance dose of 1200 mg to 1800 mg every 12 h [11]. Presently several government organizations have supported the use of the drug against mild to moderate clinical symptoms of nCOVID19

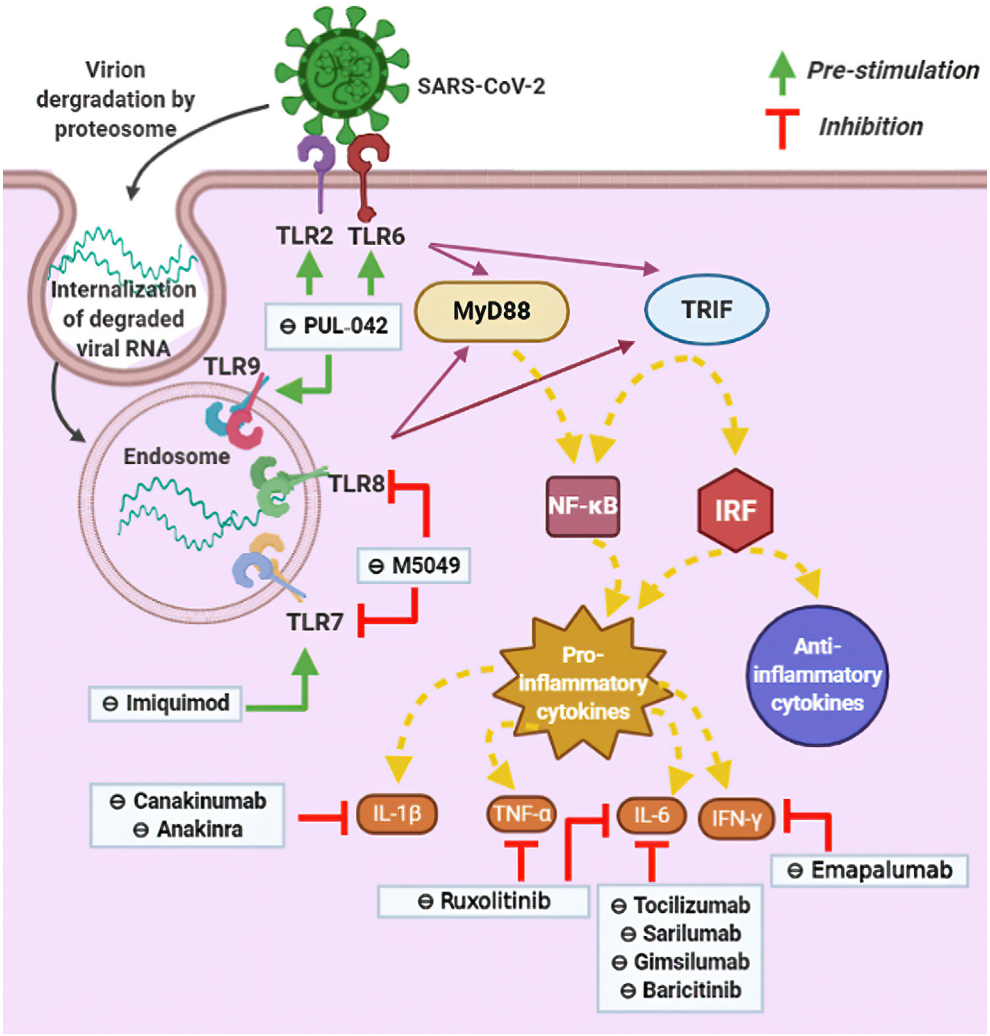

Fig. 2. Immunotherapeutic targets. The figure illustrates the various pathways of immunomodulation achieved by the different immunotherapeutic molecules.

viz. in India, Favipiravir is being jointly developed by Cipla and CSIR-IICT and is being marketed as Ciplenza for treatment of clinical features such as fever, respiratory rate, oxygen saturation and cough caused due to nCOVID19.

2.1.4. Ribavirin

Similarly, Ribavirin, a guanosine analogue was discovered by Witkowski and colleagues. It acts by outcompeting natural guanosine and consequently incorporating itself into viral RNA resulting in the induction of mutations in the viral genome, and inhibition of normal viral replication by inhibiting the RdRp activity. Nevertheless, it also exhibits its antiviral effects by inhibition of IMPDH enzyme. It has exhibited a broad-spectrum activity against RNA and DNA viruses and also has been used in the treatment of Lassa fever virus infection, Hepatitis C, influenza A and B. Several studies on Ribavirin conducted against SARS-CoV and MERS-CoV infections also promise to be quite effective and they enable it to stand as a potent candidate for fighting against SARS-CoV-2 [12,13] infections.

2.1.5. Lopinavir and Ritonavir

Formulations of Lopinavir combined along with low doses of Ritonavir have been approved by FDA for treatment against HIV infection. The formulation has been proved to be efficient against SARS-CoV and MERS-CoV infections and recent studies showcase promising results against SARS-CoV-2 infections as well [14]. A study by Chen Q *et. al.* was conducted on 9 nCOVID19 infected subjects, as they were administered with 800 mg of Lopinavir and 200 mg of Ritonavir daily, by mouth. All the patients were tested to be negative within 4–11 of treatment days and the average hospitalization period was 14.2 days for the recovery from the lung lesions, as well as from other clinical symptoms [15]. Lopinavir and Ritonavir both are anti-retroviral protease inhibitors and by studies, they are found to interact with 3-chymotripsin-like protease (3CLpro), the main protease of SARS-CoV-2 whereby Ritonavir showed a somewhat higher atomic contacts and binding efficiency with a higher number of key binding residues when compared to Lopinavir, that corresponds with lower water accessibility at the 3CLpro active site. Also, the actual metabolism of Lopinavir is retarded by Ritonavir which results in enhanced half-life and antiviral activity [16]. Side effects of the formulation are quite less severe and include gastrointestinal interference such as nausea and diarrhea, and mild hepatotoxicity. Currently, the GOIMHRD has recommended a dosage regimen for this drug combination for the clinical management of nCOVID19 and it includes Lopinavir 200 mg and Ritonavir 50 mg 2 tablets twice daily, for 7 – 14 days, also, the Spanish Society of Hospital Pharmacy has suggested a similar regimen. However, recently Cao and colleagues conducted an open-label RCT comparing the efficacy of lopinavir-ritonavir combination against standard care in 199 patients with

Table 1
Comparative summary of pharmacologic efficacy in different chemotherapeutic approaches against nCOVID19.

Agent	Plausible Mechanism	Side effects	Status
Anti-viral drugs			
Chloroquine/ Hydroxychloroquine	Inhibits the viral entry,increased efficacy with AZT	Headache, dizziness, blurred vision, difficulty hearing	Phase 4 (NCT04382625)
Remdesivir	Inhibits RdRp	Liver damage, nausea, vomiting	Completed phase 3 (NCT04292730)
Favipiravir	Inhibits viral protein synthesis	Nausea, vomiting, possible hyperuricemia and teratogenicity	Phase 2/3 (NCT04464408)
Ribavirin	Inhibits RdRp	Hemolytic anemia, teratogenicity	Phase 1 (NCT04356677)
Lopinavir/Ritonavir	Inhibits 3CLpro main protease	Drowsiness, dizziness, a bad taste in the mouth, and trouble sleeping	Phase 2 (NCT04372628)
Umifenovir	Inhibits the viral entry	Diarrhea, nausea	Phase 4 (NCT04260594)
Ivermectin	Inhibits viral replication	Joint pain and swelling, swollen and tender lymph nodes	Phase 3 (NCT04530474)
Camostat mesylate	Inhibits the viral entry	Oedema, urticaria	Phase 2 (NCT04470544)
Nitazoxanide	Inhibits viral replication, downregulates pro-inflammatory cytokines	Abdominal pain, vomiting	Phase 2 (NCT04423861)
Famotidine	Inhibits 3CLpro main protease	Stomach pain, heartburn	Phase 3 (NCT04504240)
Adjunctive therapeutics			
Heparin or LMWH	Thromboprophylaxis	Easy bleeding and bruising, pain and redness of skin	Phase 3 (NCT04401293)
Corticosteroids (Hydrocortisone, Dexamethasone, and Methylprednisolone)	Anti-inflammatory effects	Glaucoma, oedema, mood swings, high blood pressure	Phase 3 (NCT04451174)

nCOVID19 [17]. It was reported that the period to clinical improvement was similar in both groups and no significant differences in viral clearance and in mortality rates were observed. In the given context, at present 64 clinical trials are underway for this drug formulation along with other potent drug options.

2.1.6. Umifenovir

Umifenovir also is known as Arbidol is a broad-spectrum antiviral drug that has already been approved for treatment and prophylaxis against influenza in Russia and China. While being repurposed for treatment against nCOVID19, several *in vitro* studies [18,19] were performed that suggest Umifenovir to be an efficient inhibitor of SARS-CoV-2 infection and this has gained attention and research focus around the globe. It has a unique mode of action that targets and interferes with the interaction between the spike protein [20] of the virus and its cognate ACE2 receptors on the host cell, ultimately inhibiting the membrane fusion between the host cell and the viral envelope. At present several randomized clinical trials are ongoing, especially in China aimed to evaluate the efficacy of the drug against SARS-CoV-2.

2.1.7. Ivermectin

Ivermectin is originally a broad-spectrum antiparasitic agent and is currently approved in many countries for the management and treatment of filariasis, scabies, onchocerciasis, and strongyloidiasis. Recent *in vitro* studies performed on primate cell lines show that Ivermectin is able to reduce SARS-CoV-2 viral RNA by ~ 5000 folds within a mere 48 h [21]. Most likely Ivermectin attains these antiviral properties as it binds to the importin-α/β complex and destabilizes the importin-α/β heterodimer which is used by SARS-CoV-2 proteins to translocate into the host cell nucleus [22]. Moreover, when compared to drugs like Remdesivir and Hydroxychloroquine, studies show that Ivermectin exhibits better binding efficacy and forms much more stable complexes with the viral protein targets of the SARS-CoV-2 infection, indicating a further intricate role of it in checking the infection rates [23]. A drug combination of Ivermectin and Hydroxychloroquine has been proposed to synergistically inhibit both viral entry as well as replication, however, pharmacokinetic studies indicate very high values of EC_{50} and EC_{90} which is very difficult to attain in humans considering the toxicity concerns of the drug. Nevertheless, several clinical trials are in progress in different countries like Egypt, India, Iraq, and the USA which would provide credible details regarding the actual efficacy of Ivermectin.

2.1.8. Camostat mesylate

Camostat meyslate (CM) is a protease inhibitor initially discovered in Japan and has been in usage for the treatment of chronic pancreatitis and postoperative reflux esophagitis. However, recent experiments of using CM on mouse models show promising results and, the studies indicate that for human subjects administering CM 200 mg thrice daily could provide a reduction in the magnitude of the SARS-CoV-2 infection [24]. CM inhibits viral entry into the host cell by blocking the TMPRSS2 transmembrane receptor protein [25] present on the cell. Nevertheless, further *in vitro* studies and RCTs are underway to confirm the results and enable us with deeper details of its antiviral properties.

2.1.9. Nitazoxanide

In 2002 Nitazoxanide was first approved in the USA for treatment of diarrhea and enteritis. It has also been used as a first-line broad-spectrum antiviral drug which was used against the treatment of influenza in patients. In several *in vitro* studies, it is also been shown to be effective against MER-CoV and SARS-CoV-2 [26]. It functions via various mechanisms including inhibition of N protein expression of the virus; suppression of pro-inflammatory cytokines and IL-6 production as well as blocking of the viral replication [27]. However, further clinical evidence is awaited to confirm actual efficacy of the drug in patients.

2.1.10. Famotidine

Famotidine is a histamine-2 receptor antagonist and is used in the treatment of GERD, and peptic ulcer disease, however, it has also shown to be effective against HIV infection. Recent studies [28] on patients who were hospitalized with infection of nCOVID19 suggest that the use of Famotidine was associated with a reduction in the risk of clinical deterioration and mortality especially in cases with pulmonary involvement. The observation was in fact sup-

Table 2
Summary of different immunotherapeutic interventions against nCOVID19.

Agent	Plausible Mechanism	Status
Immunomodulatory agents		
Canakinumab	Inhibits IL-1β	Phase 3 (NCT04362813)
Anakinra	Inhibits IL-1β	Phase 2/ 3 (NCT04443881)
Emapalumab	Inhibits IFN-γ	Phase 2 (NCT04339712)
Tocilizumab	Inhibits IL-6	Phase 2 (NCT04317092)
Sarilumab	Inhibits IL-6	Phase 2 (NCT04280588)
Gimsilumab	Inhibits IL-6	Phase 2 (NCT04351243)
Baricitinib	Inhibits IL-6	Phase 2/3 (NCT04340232)
Ruxolitinib	Inhibits IL-6 and TNF-α	Phase 2 (NCT04334044)
PUL-042	Pre-stimulation of TLR2, 6, and 9	Phase 2 (NCT04312997)
M5049	Inhibits activation of TLR7 and TLR8	Phase 2 (NCT04448756).
Imiquimod	Pre-stimulation of TLR7	Pre-clinical trials proposed
Plasma therapy		
Convalescent		immunoglobin therapy
Promotes viral clearance	Phase 3 (NCT04372979)	
Vaccines		
Bacillus Calmette-Guerin (BCG)	Live attenuated vaccine	Phase 3 (NCT04327206)
CoronaVac	Inactivated virus vaccine	Phase 3 (NCT04582344)
Covaxin (BBV152)	Inactivated virus vaccine	Phase 3 (NCT04471519)
EpiVacCorona	Protein sub-unit vaccine	Phase 2 (NCT04527575) (Approved for public use in Russian Federation)
AdimrSC-2f	Protein sub-unit vaccine	Phase 1 (NCT04522089)
Sputnik V (Gam-COVID-Vac)	Non-replicating viral vector vaccine	Initial Phase 3 (NCT04530396) (Approved for public use in Russian Federation)
JNJ-78436735 (Ad26.COV2. S)	Non-replicating viral vector vaccine	Phase 3 (NCT04505722)
AZD1222 (Covishield)	Non-replicating viral vector vaccine	Phase 3 (NCT04516746)
Ad5-nCoV	Non-replicating viral vector vaccine	Phase 3 (NCT04526990)
ZyCoV-D	DNA-based vaccine	Phase 3
mRNA-1273	mRNA-based vaccine	Phase 3 (NCT04470427)
Tozinameran (BNT162)	mRNA-based vaccine	Phase 2/3 (NCT04368728)(Approved for public use in the UK, Bahrain, the UAE, Canada, the USA and Mexico)

ported by a computer modelling study by Wu et al. which states that the drug is able to inhibit cellular proliferation and replication SARS-CoV-2 by binding to the 3-chymotrypsin-like protease (3CLpro) [29] i.e. the main protease of the virus. Nevertheless, further *in vitro* and clinical studies are required to understand its effectiveness against nCOVID19.

2.2. Adjunctive therapeutics

Currently, with no precise treatment strategy in vision, it is of utmost priority for healthcare professionals to perform medical management of the clinical manifestations of nCOVID19 and this review aims to present some select drugs on the same.

2.2.1. Heparin

The Hyper-inflammatory state produced as a result of the cytokine storm further induces a coagulopathy cascade and in patients, there have been evidences of ischemia in the hands [30], in the lower limbs, and bilateral cerebral infarctions in different vascular territories. Heparin or LMWH has been found particularly helpful in relieving such severe complications and has been now in clinical use for prophylaxis and treatment of the same, and this was found especially effective in patients who meet the criteria for sepsis-induced coagulopathy (SIC). Moreover, studies have also found that the structural diversity of Heparin could also enable it to interfere with viral entry of SARS-CoV-2 [31], histone neutralization, chemokine binding, and leukocyte trafficking.

2.2.2. Corticosteroids

The cytokine storm is a phenomenon having multiple facets and all are needed to be addressed for reduction of mortality rates due to nCOVID19. Corticosteroids like Hydrocortisone, Dexamethasone, and Methylprednisolone have superior anti-inflammatory, antifibrotic, and vasoconstrictive effects to object hyper-inflammation and especially acute lung injury and ARDS caused by it. Administration of corticosteroids comes with its own risks including delayed viral clearance from the respiratory tract and blood, risk of secondary infections, and high rates of complications like avascular necrosis, psychosis, and hyperglycemia but clinical experiences suggest risks outweigh the benefits caused by it. However, in 2019, a *meta*-analysis of 10 observational studies with 6548 subjects infected with influenza pneumonia demonstrated that corticosteroids were associated with an increased risk of mortality [32]. Nevertheless, at present WHO guidelines discourage usage of corticosteroids against patients with non-severe forms of COVID19 [33] but also urges countries to maintain sufficient stocks of them for treatment of the same.

3. Immunotherapeutic interventions

nCOVID19 seems to have no cure by conventional chemotherapeutic approaches and herd immunity [34] promises to be the only strategy available for containing the outbreak. Metabolomic composition of SARS-CoV-2 such as proteins and nucleic acid components function as different (Pathogen-associated molecular pattern molecules) PAMPs and are detected by toll-like receptors (TLRs). TLRs are transmembrane proteins borne either intracellularly or on extracellular surfaces, studies suggest that surface TLRs like TLR1, TLR6, and especially TLR4 are involved in the detection of the viral spike protein. Contrastingly, the positive sense RNA genome of the virus constitutes for the immunogenic oligonucleotide PAMPs that are shown to be detected by various intracellular TLRs *viz.* TLR3, TLR7, TLR8 and TLR9. Once the detection is made, they activate various signaling cascades finally resulting in production of various pro-inflammatory cytokines in enormous amounts [35]. The immunological machinery is turned against patient himself generating severe complications including ARDS and severe hypoxemia. This condition can be relieved only by modulating various components of this system by different immunotherapeutic approaches, as we shall see.

3.1. Immunomodulatory agents

As discussed earlier different components of cellular PAMP detectors, cytokines and their receptors orchestrate the amplified immune response that result in the phenomenon of the cytokine storm and these therapeutic agents [36] function to inhibit such response pathways.

3.1.1. Canakinumab, and Anakinra

IL-1β cytokine poses a credible target for immunomodulation against nCOVID19 [37]. Canakinumab is a human anti-IL-1β mon-

oclonal antibody developed by Novartis, used for treatment against systemic juvenile idiopathic arthritis and active Still's disease, however, at present it is undergoing phase 3 RCTs (NCT04362813) against nCOVID19. Anakinra on the other hand is a recombinant and slightly modified version of the human IL-1β receptor antagonist protein [38] and is being tested (NCT04443881) for its effectiveness against the pandemic [39].

3.1.2. Emapalumab

Emapalumab is a human monoclonal antibody against IFN-γ and functions by blocking its binding to cell surface receptors [40]. It is under phase 2 clinical trials along with Anakinra in NCT04339712.

3.1.3. Tocilizumab, and Sarilumab

Tocilizumab, also known as Atlizumab is a humanized monoclonal antibody that functions against the IL-6 receptor [41]. It is used mainly for the treatment of systemic juvenile idiopathic arthritis and rheumatoid arthritis [42]. However, recent studies illuminate its efficacy against nCOVID19 infection and phase 2 clinical trials (NCT04317092) [43] are underway for further validation of the claims. Similar functioning is observed with Sarilumab [44,45], which is also undergoing phase 2 of clinical trials (NCT04280588).

3.1.4. Gimsilumab

Following infection by SARS-CoV-2, $CD4^+$ T lymphocytes are activated to become pathogenic T helper T_h1 cells which consequently precipitate Granulocyte-macrophage colony-stimulating factor (GM-CSF) that in turn upregulates inflammatory $CD14^+$ and $CD16^+$ monocytes having high expression levels of IL-6 that further accelerates the inflammation [46]. Gimsilumab is a monoclonal antibody that functions against the GM-CSF. It is currently being tried for lung injury or ARDS produced by COVID-19 [47], in a phase 2 RCT (NCT04351243).

3.1.5. Baricitinib

It is a powerful inhibitor of JAK-STAT signaling pathways as well as of AP2-associated protein kinase 1(AAK1) [48]. It downregulates IL-6 expression levels while it also inhibits clathrin-mediated endocytosis of the virus and thereby retards further infection of cells. Its phase2/3 clinical trial against nCOVID19 [49] is under progress (NCT04340232).

3.1.6. Ruxolitinib

Ruxolitinib is a small drug and functions as a Janus kinase (JAK) inhibitor [50] and is used in the treatment of myeloproliferative neoplasms. It is proven to counteract response generated by amplified levels IL-6 and TNF-α as observed in the phenomenon of the cytokine storm [51]. At present is it undergoing a phase 2 trial in NCT04334044, as further details are awaited.

3.1.7. Pul-042

PUL-042 is a combination of two ligands immunostimulatory ligands Pam2CSK4 (Pam2) and an oligodeoxynucleotide (ODN). Pam2 functions as an agonist to TLR2 and TLR6 while the ODN agonizes TLR9 [52,53,54]. Pre-stimulation of the said receptors provides a potent mechanism to generate prophylaxis in uninfected subjects. A PUL-042 inhaler type solution is currently being studied for its effects against nCOVID19 in trials of NCT04312997.

3.1.8. m5049

M5049 is a small molecule drug developed by Merck, it is the first of its class responsible for inhibiting activation of TLR7 and TLR8 [55] which are intracellular endosomal sensors of viral ssRNA, thereby aborting its inflammatory signaling pathway [56]. Currently, the drug is undergoing phase 2 trials (NCT04448756).

3.1.9. Imiquimod

Imiquimod (IMQ) is a drug approved by the FDA in 1997 for the treatment of genital warts, actinic keratosis, and superficial basal cell carcinoma. It functions as an immunostimulant and is responsible for activation of TLR7 [57] and consequent expression of IFN-α, IL-6, and TNF-α, and is a potent agent for prophylaxis against nCOVID19 [58]. However, further *in vitro* and clinical investigations are warranted for further understanding of the antiviral effects of the drug.

3.2. Convalescent immunoglobin therapy

In the light of current circumstances and paucity of efficient therapeutics against nCOVID19, the FDA has now approved Convalescent immunoglobin therapy or Convalescent plasma therapy citing the high potency and safety of the derived human monoclonal antibodies [59,60]. The rationale behind this therapeutic approach is that plasma containing hyperimmune antibodies are donated from patients who have already recovered from SARS-CoV-2 infection, this in turn is transfused into patients who have been infected recently and it is believed to help with free virus as well as infected cell immune clearance. Administration of plasma therapy has been found to be associated with a reduction in mortality rates with relatively few adverse effects. Serological analyses show that IgA & IgM antibodies appear in COVID-19 patients within 5 days after onset of symptoms, while IgG levels are generally detected by the 14th day and the SARS-specific antibodies have been observed to persist for as long as 2 years in the patients [61]. Nevertheless, the therapy is believed to benefit primarily within the first 7 to 10 days of infection, while its the peak of nCOVID19 viremia and generation of no significant primary immune response has taken place [62]. However, the primary contradictions regarding the therapy arise from the allergy of the recipient towards plasma protein or sodium citrate [63], though various forms of contradictions including concurrent viral or bacterial infections and thrombosis are also reported in different trial settings. While WHO has directed guidelines for screening of donors to discourage any form of anemia in them, also different approaches of manufacturing processes are being explored to improve the safety of the therapy. Finally, it is a life-saving intervention and has become indispensable in this emergency scenario.

3.3. Vaccination strategies

With over 170 countries engaged in the process, vaccine development is currently a domain of enormous research focus since it proves to be instrumental in enabling herd immunity and finally containing the outbreak. The genome of the virus is composed of a 29.9 kb (+) ss RNA, more than two-thirds of the genome possesses ORF1ab encoding mainly the non-structural proteins [64] and one-third of the genome codes for five major structural proteins of the virus [65]. One such protein is the E or envelope protein enables assemblage and release of the virus. S or spike protein is a homotrimeric protein that forms the characteristic spike structure of the virus. Generally, the S protein is cleaved by furin-like protease present in the host cell, it produces two subunits – the S1 subunit which composes the receptor-binding domain (RBD) of the spike protein and the S2 subunit which forms the stalk of the spike. The spike protein is key for ACE2 receptor-mediated endocytosis and consequent entry of the virus into the host [66,67]. M or membrane protein is the most abundant protein of the virion structure. It provides shape to the virion by promoting membrane curvature, and at the same time, it also binds to the nucleocapsid. The N-protein represents the only type of protein present in the nucleocapsid and helps to package the genome into the virion. The fifth structural protein is the hemagglutinin-esterase (HE). It acts as a hemagglutinin and binds

sialic acids on surface glycoproteins, it has acetyl-esterase activity and is thought to enhance the S protein-mediated endocytosis of the virus and enables it to spread through the mucosa. Exploiting such structural proteins as an essential source of antigenic determinants several different molecular platforms have been developed and adopted into vaccination approaches, such as non-replicating viral vectors, peptides, recombinant proteins, live attenuated viruses, inactivated viruses as well as DNA based and RNA based vaccines as described in later sections. However, this article attempts to analyze select strategies and vaccination candidates that are in advanced phases of their trials.

3.3.1. Live attenuated vaccines (LAVs)

This platform relies on whole, disarmed but live virus particles that are administered t elicit an immune response by inducing TLR sensors. They are strong and produce long-lasting immunity against the virus but require extensive trials and testing for establishing its efficacy and safety. One of the exemplary vaccine candidates that rely on this strategy is the age-old Bacillus Calmette-Guerin (BCG) vaccine [68] which is currently undergoing phase 3 trials (NCT04327206) in an effort to protect health workers against nCOVID19. It has been shown to emulate immunogenicity against peptides derived from the ORF1ab gene of SARS-CoV-2 [69].

3.3.2. Inactivated viruses

These vaccines are prepared from virus particles that have been killed and lost the capacity to infect its host. They are more stable and safer as compared to LAVs but have weak immunogenic effects and require multiple booster shots to maintain the standing immunity, however, they can be used along with adjuvants that help increase their immunogenicity. One such vaccine against nCOVID19 is CoronaVac developed by Sinovac, it is formalin-inactivated and armed with alum adjuvants [70]. Currently, it is undergoing phase 3 clinical trials with 9,000 subjects. Similarly, Indian Counsel of Medical Research (ICMR) in association with Bharat Biotech has developed BBV152 [71] (also known as Covaxin) and functions in the same principle and its ongoing phase III clinical trials have reported 81% efficacy rates among 25,800 participants (NCT04471519) (https://doi.org/10.1016/S1473-3099(21)00045–1).

3.3.3. Protein Sub-unit vaccine

This form of vaccine consists of synthetic peptides or recombinant antigenic proteins essential to emulate the immunogenicity of the original virus particle and consequently trigger a therapeutic immune response, such proteins may include the spike 'S' protein of SARS-CoV-2 which constitutes the most significant component in the nCOVID19 infection cycle. AdimrSC-2f by Adimmune [72] is such a vaccine that uses the spike protein antigenicity. It is currently within phase I of its study with 70 healthy volunteers. EpiVacCorona by Vector Institute in Siberia is another vaccine of this class and is the second vaccine after Sputnik V that is approved for public use by the Russian Ministry of Health [73]. However, it is still under phase 2 clinical trials (NCT04527575) and yet to be recognized worldwide.

3.3.4. Non-replicating viral vector vaccine

Non-replicating vector vaccines consist of a recombinant virus that enters its host cells and produces the vaccine antigens, but no new virus particles are formed. However, as they result in the production of endogenous antigen, they stimulate both humoral and cellular immune responses. They exhibit a highly specific and rapid gene delivery mechanism into the host cell and trigger a vigorous immune response. Belonging to this class, Gam-COVID-Vac (better known as Sputnik V) [74] developed by Gamaleya Research Institute of Epidemiology and Microbiology, is the first nCOVID19 vaccine to be available for public administration and functions by expressing viral S protein. Though it has attained modest approval from the Health Ministry of the Russian Federation, it is yet to undergo phase 3 trials and rigorous screening procedures prior to achieving any international recognition. Another vaccine using this technology is JNJ-78436735 by Johnson & Johnson which is announced to go through its phase 3 trials with 60,000 subjects. Functioning against the same spike protein of SARS-CoV-2 is the AZD1222, also known as Oxford–AstraZeneca COVID-19 vaccine that is being marketed as Covishield in India [75]. It has been developed jointly by Oxford University and AstraZeneca, and after a phase III trial with 30,000 participants (NCT04516746) it has now been approved for public use use by Medicines and Healthcare products Regulatory Agency. Similarly, Ad5-nCoV developed by CanSino Biologics is under phase III clinical trials with 40,000 people (NCT04526990) in Pakistan and China.

3.3.5. DNA-based vaccines

DNA vaccine is one of the most revolutionary vaccine technologies evolved throughout. It encodes both the antigen along with an adjuvant and attempts to induce the adaptive immune response, furthermore, they can be developed at an accelerated pace. The host cells so transfected cells by generally using a plasmid, thereby they initiate expression of the transgenes which essentially provide a steady supply of the transgene specific proteins that emulate the original antigenic proteins of the live virus. Moreover, as the antigenic material is endocytosed by the dendritic cells that in turn present the antigen to the $CD4^+$ and $CD8^+$ T cells while in cooperation with MHC II and MHC I antigens on the surface thus stimulate efficient cellular as well as humoral responses. One such vaccine candidate is ZyCoV-D developed by Zydus Cadila – an Indian firm [76]. It generates immunogenicity against membrane 'M' protein and at present, it has been permitted by Drugs Controller General of India (DCGI) to undergo its phase III trials with 26,000 Indian participants.

3.3.6. mRNA-based vaccines

mRNA-based vaccine is yet another emergent, non-integrating, and non-infectious platform which poses no potential risk of insertional mutagenesis. These vaccines comprise of non-replicating RNA strands generally encapsulated in lipid-based nanoparticles, and as they enter their host machinery they initiate their expression and thereby mimic the antigenic patterns that is usually observed throughout the course of the natural infection pathway of the virus. It enables rapid vaccine development and is a powerful strategy in the current times of the pandemic. mRNA-1273 by Moderna [77] and Tozinameran (BNT162) by Pfizer & BioNTech [78] are such candidates using the said platform. The mRNA-1273 encodes viral S protein and has advanced to its phase 3 trials (NCT04470427) which would consist of 30,000 individuals, On the other hand, Tozinameran has exploited precisely the RBD of the spike protein for generating antigenic determents and currently is going through it phase 2/3 trials (NCT04368728) also having a proposed size of 44,000 subjects, however, it has attained approval for use in the UK, Bahrain, the UAE, Canada, the USA and Mexico.

4. Discussion

So far, no ubiquitous cure could have been found to the disease, however, various treatment regimens have been developed and many of them have been known to be functional in impeding the infection. Early understanding of coronaviruses like SARS-CoV and MERS-CoV proved to be critical in gaining insights of the infections of SARS-CoV-2, while repurposing of old drugs against the pandemic was a rapid response strategy used to withstand the infection. Credible vaccination strategies promise to be the only

therapy to enable herd immunity and finally contain the infection. At present, only a few of the vaccine candidates have been approved only in certain regions of the world, however, such interventions are far from being lucidly available and accessible to public globally, given the extensive time periods essential for establishing the safety and efficacy of the vaccine candidates and even for quality mass synthesis of the successful candidates. In this context, several therapeutic strategies have evolved which mainly comprise of two approaches – the chemotherapeutic approach that functions against the viral pathology and involves direct interaction of the administrated xenobiotic drugs against the incoming virus and deterring its infection cycle, anti-viral drugs like Hydroxychloroquine, Remdesivir, Favipiravir interrupt the viral invasion and its cellular proliferation by interacting with different key enzymes responsible for the process. Additionally, Heparin and Corticosteroids provide for the supportive medicine to the patient and deals with the damage produced by the infection. Chemotherapeutic drugs prove to be appropriate for providing a functional and rapid treatment choice but fails to provide a drastic and long-lasting resistance from the infection, nevertheless, there exists a second approach in form of immunotherapy that involves modulation of the various components of our own immune system and sophisticatedly directing it towards containing the infection and enhancing viral clearance. Different immunomodulatory agents have been shown to partake in the process, whereby agents like Canakinumab and Tocilizumab function to inhibit the IL-1β and IL-6 syntheses and consequently retard the cytokine storm caused by the infection. Similarly, PUL-042 and IMQ are known to produce pre-stimulation of various TLRs and promote viral clearance. Research on both the approaches are proceeding at a rapid pace and has provided us with various anti-viral drugs, it has reduced the mortality rates by improving the standard care to the infected patients. Furthermore, it has realized the excellent concept of immunomodulation that adds another dimension over functioning of conventional medicine. Different vaccination strategies have been adopted and undergoing rigorous trials for manifesting their public safety profiles, meanwhile, it is of prime importance to provide critical supportive care for the patients and to strictly follow prophylactic norms as suggested in WHO guidelines in order to deter the infection and contain its spread.

5. Conclusion

Perceiving a review on such a dynamic and powerful subject has been justly a laborious yet heartening experience. The current pressure mounted on the research community has led to the generation of very good hypotheses and experiments along with some poorly designed studies, and biased conclusions. Given the superabundant amount of literature on the one hand and the dearth of critical therapeutics on the other, comprehensively covering such highly sensitive research topics with wariness was the primary goal to our work. This article reveals the present terrain of the therapeutic approaches against nCOVID19. Though many of the treatment approaches seem to be functional in retarding the infection, the need of the time is to develop more numbers of combinatorial therapy regimens involving chemotherapy as well as vaccination strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' Contributions

AC wrote the manuscript. GM assisted in writing the manuscript. SM designed the study, drafted and edited as well as finalized the manuscript.

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