SARS-CoV-2 Clinical Trial Results

Subjects: Infectious Diseases

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The coronavirus disease 2019 (COVID-19) pandemic has claimed over 7 million lives worldwide, providing a stark reminder of the importance of pandemic preparedness. Due to the lack of approved antiviral drugs effective against coronaviruses at the start of the pandemic, the world largely relied on repurposed efforts. Here, the researchers summarise results from randomised controlled trials to date, as well as selected in vitro data of directly acting antivirals, host-targeting antivirals, and immunomodulatory drugs. Overall, repurposing efforts evaluating directly acting antivirals targeting other viral families were largely unsuccessful, whereas several immunomodulatory drugs led to clinical improvement in hospitalised patients with severe disease. In addition, accelerated drug discovery efforts during the pandemic progressed to multiple novel directly acting antivirals with clinical efficacy, including small molecule inhibitors and monoclonal antibodies.

Keywords: COVID-19 ; SARS-CoV-2 ; coronavirus ; therapeutics ; clinical trial ; drug discovery

1. Directly Acting Antivirals (DAA)

Directly acting antivirals (DAA) that include small molecules and some antibodies, target virally encoded proteins directly and efficiently suppress viral replication in vivo [1] (reviewed in [2][3]). DAA commonly targets viral entry and fusion, or key enzymes like viral polymerases and proteases such as the SARS-CoV2 3-chymotrypsin-like protease (3CL^{pro}), also known as main protease (M^{pro}), and papain-like protease (PL^{pro}) [1][3]. By targeting viral replication directly, DAA are generally thought to have fewer side effects than HTA [4]. However, by targeting the virus directly, DAA are known to cause mutations that can lead to reduced drug efficacy and drug resistance [5][6].

Rapid SARS-CoV-2 small molecule drug discovery efforts were carried out during the 2019 SARS-CoV-2 pandemic, targeting the viral polymerase (remdesivir, Gilead; molnupiravir, Merck, and others) and main protease (nirmatrelvir, Pfizer; ensitrelvir, Shionogi; and others). The pandemic also gave rise to innovative and collaborative approaches such as collaborative alliances across biopharmaceutical companies creating public–private partnerships such as the Innovative Medicines Initiative Corona Accelerated R&D in Europe (https://www.imi-care.eu/, accessed on 8 November 2023), close-knit consortia of companies, and even completely open science consortia with company participation such as the COVID Moonshot [7][8].

1.1. Protease Inhibitors

SARS-CoV-2 M^{pro} has been a drug development target from early in the pandemic, with numerous novel SARS-CoV-2 inhibitors in the clinical and preclinical pipeline. Two SARS-CoV-2 M^{Pro} inhibitors are now under EUA, including nirmatrelvir/ritonavir (brand name Paxlovid) and ensitrelvir (brand name Xocova).

The covalent SARS-CoV-2 M^{pro} inhibitor nirmatrelvir (PF-07321332) developed by Pfizer is available in combination with ritonavir (available as Paxlovid) and has been evaluated in multiple RCTs to date. Nirmatrelvir showed potent antiviral activity in in vitro assays, with a half-maximum effective concentration (EC_{50}) of 231 nM in Vero E6 cells [9]. In RCTs, when nirmatrelvir/ritonavir was given within three days of symptoms onset, nirmatrelvir-treated individuals had a significantly reduced risk of severe COVID-19 in comparison to placebo-treated controls, alongside reduced viral loads at day five of treatment [10]. A recent phase 2 RCT study result revealed that nirmatrelvir/ritonavir was more effective than the other leading oral antiviral drug for patients with COVID-19 [11]. A drawback of the combination with the pharmacokinetic (PK) enhancer ritonavir are significant drug-drug interactions, preventing the use in patients with severe renal or hepatic impairment [12][13][14]. A second-generation broad-spectrum protease inhibitor, PF-0781883 has been recently disclosed by Pfizer and is currently in Phase 2 clinical trials, with an initial human PK profile suggesting no further need to co-administer with ritonavir [15].

Ensitrelvir (S-217622) was developed by Shionogi as an oral noncovalent nonpeptidic M^{pro} inhibitor of SARS-CoV-2 using virtual and biological screening of compound libraries and a structural-based drug design strategy of the hit compounds [16][17]. In comparison to nirmatrelvir/ritonavir, ensitrelvir shows an optimized PK profile [17] and displays potent in vitro antiviral activity against SARS-CoV-2 variant of concern (VOC) including Delta (EC_{50} = 34.8 nM) and Omicron BA.1 (EC_{50} = 23.9 nM) variants, as well as other coronaviruses: SARS-CoV-1 (EC_{50} = 0.21 µM), MERS-CoV (EC_{50} = 1.4 µM), and HCoV OC43 (EC_{90} = 0.074 µM) [17][18]. Ensitrelvir is progressing to Phase 2/3 clinical trials. Results disclosed from the Phase 2a trial showed a significant reduction in viral titer and RNA on day four, a median time of negative RT-PCR conversion of two days, and acceptable adverse events [19]. This drug recently received emergency regulatory approval from the Ministry of Health, Labour and Welfare of Japan, with ongoing Phase 3 clinical trials and plans to extend the approval for worldwide use.

Other oral main protease inhibitor candidates in clinical trials include PBI-0451 from Pardes Biosciences and EDP-235 from Enanta Pharmaceuticals [20]. In addition, novel initiatives like the crowdsourced open-science effort COVID Moonshot brought together academic and industrial partners from across the world to develop SARS-CoV-2 M^{pro} inhibitors [8][21]. More than 2400 molecules were synthesised and rapidly shared to create a rich intellectual property-free dataset. The search for a potent covalent COVID-19 M^{pro} inhibitor has also been aided by a computational pipeline to efficiently identify irreversible inhibitors [21]. Due to its open access and free data-sharing nature, the Moonshot fragment dataset may have aided in the early development of the Shionogi M^{pro} compound.

Due to its saliency as a target, repurposing efforts early in the SARS-CoV-2 pandemic focused on the M^{pro}. Repurposed protease inhibitors evaluated in RCTs include lopinavir (with and without ritonavir), darunavir, and danoprevir; however, none of the tested inhibitors showed efficacy against SARS-CoV-2.

Lopinavir is a protease inhibitor that has been developed for the treatment of human immunodeficiency virus (HIV) and is used in combination with the PK enhancer ritonavir that blocks the enzyme cytochrome P450 3A [22]. Lopinavir showed some in vitro activity against both SARS-CoV-1 and SARS-CoV-2 with half maximum inhibitory concentrations (IC_{50}) of 50 and 26 µM, respectively [22]. Lopinavir/ritonavir was assessed in multiple COVID-19 RCTs, however, it failed to show any clinical benefit and is therefore not recommended as COVID-19 standard care for hospitalised patients [23][24].

Darunavir is another inhibitor of the HIV protease that is in clinical use in combination with the PK enhancer cobicistat [25]. Darunavir was not active against SARS-CoV-2 in vitro at clinically relevant concentrations [26] and in line with these results, did not show clinical efficacy in COVID-19 RCTs.

Danoprevir, a hepatitis C virus (HCV) protease (NS3/4A) inhibitor that is used in combination with ritonavir [27] showed cellular activity against SARS-CoV-2 with an EC_{50} of 87 µM in Vero E6 cells [28]. In hospitalised patients infected with SARS-CoV-2, danoprevir with ritonavir shows a good safety profile [27] with shorter times to PCR negativity and shorter hospital stays compared to the lopinavir/ritonavir group [29].

1.2. RNA-Dependent RNA Polymerase (RdRp) Inhibitor

The RNA-dependent RNA polymerase (RdRp) is essential for viral replication and is highly conserved among coronaviruses and positive-strand RNA viruses, and a clinically validated target across many viruses [30][31]. Several existing RdRp inhibitors developed against other RNA viruses, including remdesivir [32][33], molnupiravir [34], and favipiravir [35], were in late-stage development or clinical use at the start of the pandemic and showed promising in vitro activity against the SARS-CoV-2. Subsequently, numerous clinical trials were conducted to explore their potential against SARS-CoV-2 infection.

Remdesivir is a nucleotide analogue inhibitor of the RdRp that was originally developed for the Ebola virus (EBOV) [36]. It shows potent broad-spectrum antiviral activity against pathogenic animal and human coronaviruses in vitro [32][33][37]. However, remdesivir's intravenous administration limits its widespread use in the community. Based on multiple clinical trials, remdesivir was the first antiviral drug approved for the treatment of COVID-19 in adults and paediatric patients (≥28 days old and weighing ≥ 3 kg) with a positive SARS-CoV-2 test, for both hospitalised patients, and non-hospitalised individuals with mild-to-moderate COVID-19 that are at high risk for progression to severe COVID-19 [38]. One randomised, double-blind, placebo-controlled clinical trial (ACTT-1 study) showed a shorter median time to recovery for remdesivir-treated patients compared to placebo [39]. Two additional trials sponsored by Gilead Sciences informed the approval. An open-label clinical trial of hospitalised adults with moderate COVID-19 showed an improvement in symptoms in patients receiving a five-day course of remdesivir, however, no improvement was demonstrated in those receiving a 10-day course of remdesivir [40]. A third randomised, open-label trial in hospitalised adults with severe COVID-19 showed no statistically significant differences in recovery or mortality rates [41]. However, it is important to note that with DAA, initiating

treatment early whilst viral loads are high is crucial for compound efficacy, and variable treatment windows may explain conflicting clinical trial results [42]. An oral pro-drug of remdesivir, obeldesivir, shows excellent cross-reactivity against multiple coronaviruses including MERS, in vitro [43]. A recent Phase 3 RCT to evaluate the efficacy and safety for the treatment of COVID-19 in non-hospitalised patients with a high risk for disease progression was discontinued due to lower than expected incidence rates and related hospitalisations or all-cause death, whilst a Phase 3 RCT in hospitalised patients is still ongoing [44].

Molnupiravir is an orally available RdRp inhibitor with broad-spectrum antiviral activity [34] and was initially developed as an oral antiviral against Venezuelan equine encephalitis virus (VEEV) [30]. It acts as a nucleoside analogue in the RNA elongation process where it incorporates mutation errors that accumulate into an “error catastrophe” and subsequent virus replication failure [30][34][45]. Molnupiravir is authorised for emergency use for SARS-CoV-2 infection by the FDA in adults with confirmed mild-to-moderate SARS-CoV-2 infection, including those who are at high risk for progression to severe disease and those for whom alternative treatment options are not accessible or clinically appropriate. The FDA authorisation was based on the randomised, double-blind, placebo-controlled MOVe-OUT trial, demonstrating a reduction in hospitalization and mortality in the molnupiravir-treated group compared to the placebo [46]. However, the European Medicines Agency refused market authorisation for molnupiravir [47], arguing that it was not possible to conclude that molnupiravir reduces the risk of hospitalisation or death in adults at risk of severe disease.

Several other RdRp inhibitors that have been developed for other viral infections have been investigated for clinical efficacy in COVID-19 as part of intensive repurposing efforts. Favipiravir is a guanine analogue that selectively inhibits the RdRp and has been developed as a novel antiviral compound against influenza by Toyama Chemical Co. Favipiravir has been evaluated against SARS-CoV-2 infection in multiple clinical trials, with no significant effects on hospitalisation and mortality even when administered within 5 days of symptoms developing [48]. Sofosbuvir, a potent inhibitor developed against the RdRp of HCV, has and is in clinical use in combination for the treatment of chronic HCV infection in combination with ribavirin, ledipasvir, and daclatasvir for different genotypes. In multiple RCTs conducted with sofosbuvir in SARS-CoV-2 infection, no effect on endpoints was observed, apart from a small open-label study demonstrating an effect on median hospital stay [49]. Azvudine, a nucleoside analogue RdRp inhibitor originally developed against HIV infection [50][51] has been approved for the treatment of COVID-19 by the Chinese regulatory agency in 2022, citing a phase 3 clinical trial showing “improved clinical symptoms”, compared to a placebo [52][53]. However, detailed clinical trial data has not been published to date. Publicly available data is limited, with studies available showing an impact on SARS-CoV-2 viral replication and a shortened time to viral clearance in patients with mild COVID-19, compared to the standard antiviral treatment [54], as well as an impact on disease progression outcome in retrospective studies.

1.3. Monoclonal Antibodies

Neutralising monoclonal antibodies, mostly targeting the receptor binding domain (RBD) of the SARS-CoV-2 spike protein, has been tested in several clinical trials [3] and are reviewed elsewhere [55]. They offer a highly effective therapy against viral infections. However, their use is limited in clinical practice due to (i) the need for intravenous application which limits their use to hospital settings [56][57]; (ii) high costs that restrict access for large parts of the global population [58]; (iii) the reduced efficacy of some antibodies against VoCs [59]. Specifically, some antibodies with good efficacy against earlier SARS-CoV-2 variants were less potent against Omicron and its sub-variants [60]. Antibodies are effective in mild to moderate disease if given early. Further developments in the use and applicability of monoclonal antibodies for preventing COVID-19 and for early therapy are underway, including alternative applications such as nasal sprays [61].

Examples of monoclonal antibodies developed against SARS-CoV-2 include the antibody cocktail bamlanivimab with etesevimab from Eli Lilly and Company [62], Regeneron’s REGN-COV2 casirivimab and imdevimab cocktail [56][63], and the monotherapy sotrovimab by Vir Biotechnology in collaboration with GlaxoSmithKline [64].

The combination of bamlanivimab and etesevimab lowers COVID-19-related hospitalisation and mortality in mild to moderate COVID-19 cases and reduces SARS-CoV-2 viral load [65]. The use of antibody cocktails that target different neutralisation epitopes may be one way to maintain their therapeutic efficacy [66]. The non-competing monoclonal antibodies casirivimab and imdevimab bind to two different sites on the RBD of the SARS-CoV-2 spike protein resulting in the blockage of viral entry into host cells [56]. This antibody combination therapy reduced mortality at 28 days in seronegative patients but not in seropositive patients at baseline [56].

The neutralising antibody sotrovimab, developed by GlaxoSmithKline and Vir Biotechnology neutralises SARS-CoV-2 by targeting a highly conserved epitope in the RBD of the spike protein [57]. Treatment with sotrovimab reduced the risk of COVID-19 disease progression to hospitalisation or death in mild to moderate high-risk patients [57]. Sotrovimab

monotherapy retained activity against SARS-CoV-2 VOCs including Omicron [64], however, has been associated with the rapid development of spike gene mutations in vitro [59] and in vivo [64].

Bebtelovimab, developed by Eli Lilly, is a neutralising IgG1 monoclonal antibody that binds to an epitope within the RBD of the SARS-CoV-2 S protein with broad neutralising activity to all SARS-CoV-2 VOCs, including the Omicron variant [67]. Bebtelovimab has been studied in the BLAZE-4 clinical trial and is associated with greater viral clearance. It is effective for the treatment of mild to moderate COVID-19 in adults and children above 12 years old who are at risk of disease progression and hospitalisation [68].

The long-lasting monoclonal antibody combination of tixagevimab and cilgavimab (brand name Evusheld from AstraZeneca) was derived from antibodies isolated from B cells of patients infected with SARS-CoV-2 [69][70].

The FDA removed its EUA for several monoclonal antibodies including bebtelovimab, tixagevimab-cilgavimab, sotrovimab, bamlanivimab-etesevimab, and casirivimab-imdevimab [71], due to their reduced efficacy against Omicron and its subvariants that are now circulating at high frequency [59][60].

2. Host-Targeting Antivirals (HTA)

Host-targeting antivirals (HTA) are drugs that modify host cell pathways required for viral replication [72]. They often modulate virus-host interactions by targeting human proteins used by viruses. As they may target host cell pathways used by several viral families, HTAs may be suitable as a first-line antiviral drug when a novel virus emerges, provided the novel virus relies on the same host pathway. Conceptually, HTAs could be given early in a pandemic, prior to emerging virweuses being characterised at the molecular level, and may carry a lower risk of drug resistance [5][6].

2.1. Inhibitors of Viral Cell Entry

SARS-CoV-2 enters host cells by attaching to the cell membrane and subsequently fusing in the endosome. Entry requires the spike glycoprotein, which is cleaved by the host protease furin into S1 and S2 subunits during viral release from an infected cell. The subunits remain non-covalently associated and are present on mature virions as trimeric spikes. The S1 subunits bind the obligate SARS-CoV-2 receptor ACE2 with their RBDs, while the S2 subunits anchor the spike protein to the membrane and contain the fusion peptide. When S1 binds ACE2, an S2′ site within S2 is exposed and triggers its cleavage by the transmembrane serine protease 2 (TMPRSS2) at the cell surface, or by cathepsin L in the endosome after receptor-mediated endocytosis [73]. Every step in this intricate entry process is important and presents a potential DAA or HTA target.

Camostat mesylate, an inhibitor of TMPRSS2, has been reported as a potential entry inhibitor [74]. Although considered safe and well-tolerated, no clinical benefit was observed from RCTs results in terms of reduction of the disease progression or mortality.

Umifenovir (arbidol) was developed for the treatment of influenza virus as a hemagglutinin inhibitor preventing virus-mediated fusion with the cell membrane, blocking viral entry into target cells [75][76]. Unsurprisingly, as SARS-CoV-2 viral entry does not depend on hemagglutinin, RCT results evaluating its activity against COVID-19 showed no favourable effect and limited efficacy of arbidol in treating COVID-19 [77][78].

Some inhibitors work by interacting with dynamin, a GTPase responsible for clathrin-dependent endocytosis, which is essential for coronaviruses to enter the cell [79]. Chlorpromazine (CPZ), an antipsychotic medication, has been repurposed as a COVID-19 therapeutic based on this mechanism and reported for its antiviral activity against MERS-CoV and SARS-CoV-1 [80]. These findings led to a clinical trial that observed a lower incidence of symptomatic COVID-19 among patients after treatment with CPZ [81].

Disulfiram is a hepatic aldehyde dehydrogenase inhibitor that is used to treat chronic alcoholism [82][83]. It reduced the incidence and severity of COVID-19 in a retrospective observational study [82], although no impact on viral load was shown [83]. Further large-scale clinical trials are needed to assess the findings.

Fluvoxamine is a psychotropic medication that belongs to a group of functional inhibitors of acid sphingomyelinase (FIASMA) which were evaluated against COVID-19 [84]. The rationale for using FIASMA is linked to the role of lipid rafts in viral entry. Sphingomyelinase activity is triggered by SARS-CoV-2 binding which in turn leads to the formation of ceramide-enriched membrane domains that help viral entry by clustering ACE2 [85]. Treatment with fluvoxamine inhibits the sphingomyelinase activity formation of these domains in vitro [85][86]. Fluvoxamine and other FIASMA drugs were

associated with reduced mortality in COVID-19 patients were tested in a large cohort study [87]. Although three RCT studies showed favourable clinical benefits of fluvoxamine, clinical evidence was deemed insufficient to issue a treatment recommendation in the National Institutes of Health (NIH) treatment guidelines [88].

2.2. Inhibitor of Viral Glycoprotein Folding

Enveloped viruses require the glycoprotein-folding machinery in the host endoplasmic reticulum (ER) to correctly fold their glycosylated proteins [5]. Pivotal players in this ER quality control (ERQC) pathway are the ER alpha glucosidases, which can be targeted for example by iminosugars [89][90][91]. Partially inhibiting the ERQC prevents the proper folding and incorporation of viral glycoproteins into budding viruses, as shown previously for other enveloped viruses such as HIV [92], human papillomavirus [93], dengue [91][94][95], influenza [91][96], hepatitis B virus [97], HCV [98], Zika virus [99], Marburg virus [100] and EBOV [101], and could lead to a potential broad-spectrum antiviral drug also against coronaviruses. The extensively glycosylated SARS-CoV-2 spike protein is essential for viral entry, and inhibition of its proper glycosylation leads to antiviral effects. The monocyclic UV-4 (N-(9-methoxynonyl)-1-deoxynojirimycin) or MON-DNJ prevented SARS-CoV-2-induced Vero cell death and reduced viral replication in vitro after 24 h of treatment [5][102]. The results are encouraging and need to be further tested in vivo and in clinical trials.

2.3. Host-Targeting Antivirals with Unknown Mechanism

Some repurposed drugs work by targeting the host, although the exact antiviral mechanisms are unknown. Ivermectin, an FDA-approved anti-parasitic drug was reported to have an in vitro antiviral activity to SARS-CoV-2 [103]. However, several adequately powered RCTs in Brazil [104], the US [105][106], and Malaysia [107] failed to report a clinical benefit from the use of ivermectin in COVID-19 outpatients and it is not approved or authorised by the FDA for the treatment of COVID-19.

Similar attention was given to the anti-malaria drug chloroquine and its derivatives [108]. Chloroquine was reported to have efficacy and acceptable safety against COVID-19-associated pneumonia in multi-centre clinical trials conducted in China [109] and its use attracted disproportionate attention during the coronavirus pandemic, spurred by preliminary studies and endorsement from political leaders [110]. The chloroquine derivative hydroxychloroquine was tested in RCTs with limited to no clinical benefit for COVID-19 [111]. Based on sufficiently powered randomised trials [112][113] however, NIH treatment guidelines recommend against the use of both chloroquine and hydroxychloroquine for the treatment of COVID-19 [88].

The anti-protozoal drug nitazoxanide also showed in vitro activity against SARS-CoV-2 [114], and has been tested in multiple RCTs. A possible mechanism of action may be linked to inhibition of SARS-CoV-2 spike-induced syncytia and its binding to TMEM16 [115]. Nitazoxanide did not show efficacy in a number of RCTs when used at approved doses, and NIH treatment guidelines recommend against the use of nitazoxanide for the treatment of COVID-19 [88]. However, nitazoxanide did not show serious adverse events when evaluated in a Phase 1 study at higher doses of 1500 mg twice daily, at which it may provide antiviral efficacy according to the pharmacokinetic modelling [116].

3. Immunomodulatory Drugs

Immunomodulatory drugs are commonly used in autoimmune disease and include both monoclonal antibodies and small molecule inhibitors. They can either target cytokines directly, such as monoclonal antibodies against interleukins (ILs) or tumour necrosis factor (TNF)-alpha, inhibit proteins involved in inflammatory signalling pathways such as the janus kinase (JAK) inhibitors, or interfere with the hormonal regulation of inflammation such as corticosteroids [117][118]. Multiple monoclonal antibodies and immunomodulatory compounds were evaluated in COVID-19 infection, driven by the aim to impact on COVID-19 associated systemic inflammation that can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer and ferritin [119][120][121][122]. Crucial for the assessment of the effects of immunomodulatory drugs were large-scale platform trials initiated early in the pandemic.

3.1. Corticosteroids

Corticosteroids bind to the glucocorticoid receptor and inhibit the synthesis of multiple inflammatory proteins through the suppression of genes that encode them, as well as promoting anti-inflammatory signals [122][123]. Coordinated from Oxford, the open-label RECOVERY trial recruited over 43,000 hospitalised patients with COVID-19 participants worldwide and randomly assigned patients to treatment groups that included dexamethasone, hydroxychloroquine, lopinavir-ritonavir, or azithromycin, and compared them to usual care, with the primary endpoint mortality at 28 days [124]. Dexamethasone treatment significantly decreased mortality in patients who were receiving either invasive mechanical ventilation or oxygen alone at randomization [125]. Another inhaled corticosteroid, budesonide, was assessed in the PRINCIPLE study in non-

hospitalised patients with COVID-19, and improved recovery time with the potential to reduce hospital admissions or deaths [126].

3.2. Host-Targeting Monoclonal Antibodies

Multiple immunomodulatory monoclonal antibodies, directed against cytokines such as against tumour necrosis factor alpha (TNF-α), Interleukin (IL)-1, and IL-6, were assessed in COVID-19 patients [122]. Tocilizumab is a recombinant humanised monoclonal antibody that binds to interleukin-6 receptors, thereby blocking the activity of the pro-inflammatory cytokine. IL-6 is produced by a variety of cell types including lymphocytes, monocytes, and fibroblasts, and has been shown to be induced by SARS-CoV-2 infection in bronchial epithelial cells. The IL-6 inhibitor tocilizumab is in clinical use for several inflammatory diseases such as rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. As of 24 June 2021, the FDA has authorised the use of tocilizumab under EUA for the treatment of COVID-19 in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [127]. The authorisation was based on the results of 4 clinical trials: RECOVERY, EMPACTA, COVACTA, and REMDACTA, with the decision to grant EUA mainly based on the positive results of RECOVERY and EMPACTA that demonstrated an impact on mortality and a composite readout of mechanical ventilation and mortality [128][129].

IL-1 inhibitors include the IL-1 receptor antagonist Kineret (brand name anakinra), the IL-1 “Trap” rilonacept, and the neutralising monoclonal antibody to IL-1β canakinumab [122][130]. Anakinra was considered a safe and efficient treatment for severe forms of COVID-19 with a significant survival benefit in critically ill patients and features of macrophage activation-like syndrome [131][132], with most RCTs supporting the clinical benefit of this drug for COVID-19.

TNF-inhibitors have been used in severe cases of autoimmune inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, or ankylosing spondylitis [133]. Several formulations of TNF inhibitors are currently available, including adalimumab, etanercept, and infliximab [122]. Elevated serum levels of TNF-α and soluble TNF-Receptor 1 have been detected in COVID-19 patients with severe infection, providing a rationale for the use of TNF-α inhibitors in SARS-CoV-2 infection [134]. However, concerns regarding the potential suppression of antiviral immune responses have been raised by an observational study showing a negative impact on SARS-CoV-2 antibody levels following natural infection in patients with inflammatory bowel disease treated with infliximab [135][136]. In the CATALYST open-label phase 2 trial, infliximab showed no impact on CRP levels as a measure for inflammation in SARS-CoV-2 infection [137]. Recently reported results of the ACTIV-1 trial, a placebo-controlled, masked, RCT among patients hospitalised for COVID-19, reported a significant benefit of infliximab on mortality [138], but no impact on the primary study endpoint length of pneumonia [139].

The latest addition to monoclonal antibodies under EUA is vilobelimab, a monoclonal antibody that specifically binds to the soluble human complement C5a, a product of complement activation. C5a activates the innate immune response, including the local release of histamines, contributing to inflammation and local tissue damage. In vivo studies demonstrated that an anti-C5a monoclonal antibody inhibited acute lung injury in a human C5a receptor knock-in mouse model [140]. The phase 3 PANAMO RCT study recorded an improvement in invasive mechanically ventilated patients’ survival that led to a decrease in mortality with the use of vilobelimab [141].

3.3. Janus Kinase (JAK) Inhibitors

The primary mechanism of action of Janus kinases (JAK) is the phosphorylating signal transducer and activator of transcription (STAT), a key player in signalling pathways involved signalling, growth, survival, inflammation, and immune activation. Inhibiting JAK prevents the phosphorylation of key signalling proteins involved in inflammation pathways, thereby blocking cytokine signalling [122][142]. Tofacitinib and baricitinib are orally available small-molecule JAK inhibitors approved for the treatment of rheumatoid arthritis [142] and have been evaluated in multiple RCTs in patients with SARS-CoV-2 infection, leading to a treatment recommendation in hospitalised adults that require respiratory support [88]. In brief, baricitinib had an impact on mortality [143][144], as well as reducing intensive care unit admissions, lowering the requirement for invasive mechanical ventilation, and improving patients’ oxygenation index [145][146], effects that were maintained in a meta-analysis [147]. Furthermore, baricitinib in combination with remdesivir showed superior results compared to remdesivir alone in reducing patients’ recovery time and improving their clinical status [148].

In summary, for immunomodulatory drugs, the NIH issued guidelines based on the existing evidence, recommending dexamethasone, tocilizumab, and baricitinib for hospitalised patients with COVID-19, whilst the evidence for anakinra, inhaled corticosteroids, and vilobelimab was deemed inconclusive, despite all compounds receiving EUA from the FDA.

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