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# Progress, pitfalls, and path forward of drug repurposing for COVID-19 treatment

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**Abstract:** On 30 January 2020, the World Health Organization (WHO) declared the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic a public health emergency of international concern. The viral outbreak led in turn to an exponential growth of coronavirus disease 2019 (COVID-19) cases, that is, a multiorgan disease that has led to more than 6.3 million deaths worldwide, as of June 2022. There are currently few effective drugs approved for treatment of SARS-CoV-2/COVID-19 patients. Many of the compounds tested so far have been selected through a drug repurposing approach, that is, by identifying novel indications for drugs already approved for other conditions. We here present an up-to-date review of the main Food and Drug Administration (FDA)-approved drugs repurposed against SARS-CoV-2 infection, discussing their mechanism of action and their most important preclinical and clinical results. Reviewed compounds were chosen to privilege those that have been approved for use in SARS-CoV-2 patients or that have completed phase III clinical trials. Moreover, we also summarize the evidence on some novel and promising repurposed drugs in the pipeline. Finally, we discuss the current stage and possible steps toward the development of broadly effective drug combinations to suppress the onset or progression of COVID-19.

**Keywords:** antivirals, baricitinib, COVID-19, dexamethasone, drug repurposing, molnupiravir, remdesivir, SARS-CoV-2, tocilizumab

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## Key Messages

Several FDA-approved drugs have been repurposed to help treating COVID-19. Some of these, such as molnupiravir, remdesivir, dexamethasone, tocilizumab, and baricitinib have shown promising clinical results, displaying some level of efficacy in randomized controlled studies. New repurposing approaches are being tested and have displayed preclinical efficacy in animal models. Efforts are ongoing to define the best drug combinations to treat SARS-CoV-2-infected patients, both in the early stages and during severe COVID-19.

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic is the most significant global health crisis as the 1918 influenza outbreak, and it has caused enormous health and economic devastation

around the world.<sup>1</sup> The causative agent of COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a single-stranded 5'-capped positive-sense RNA virus<sup>2,3</sup> that was identified as a novel strain of group 2b of beta coronaviruses.<sup>4</sup> The viral genome ranges in size from 26 to 32 kb and contains 14 open reading frames (ORFs)<sup>2,3</sup> that encode for both structural and nonstructural proteins, as well as for several accessory proteins (Figure 1). The structural proteins include a helical nucleocapsid surrounding the viral genome, the spike (S) glycoprotein, which is essential for viral attachment and entry, and the membrane (M) and the envelope (E) proteins that are mainly required for viral assembly and viral envelope formation.<sup>5,6</sup> The nonstructural proteins include key enzymes necessary for viral replication, such as the viral proteases and the RNA-dependent RNA

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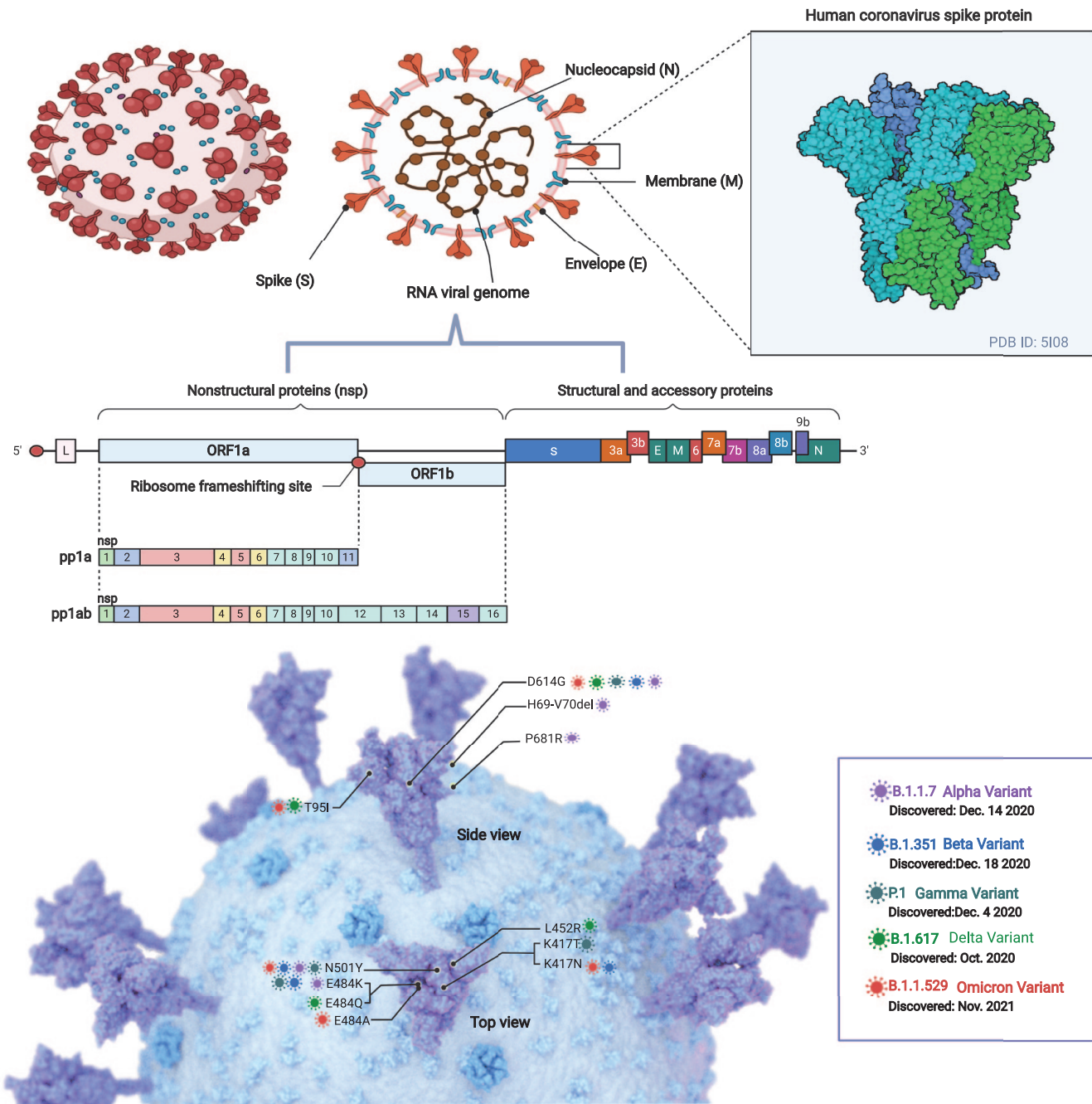
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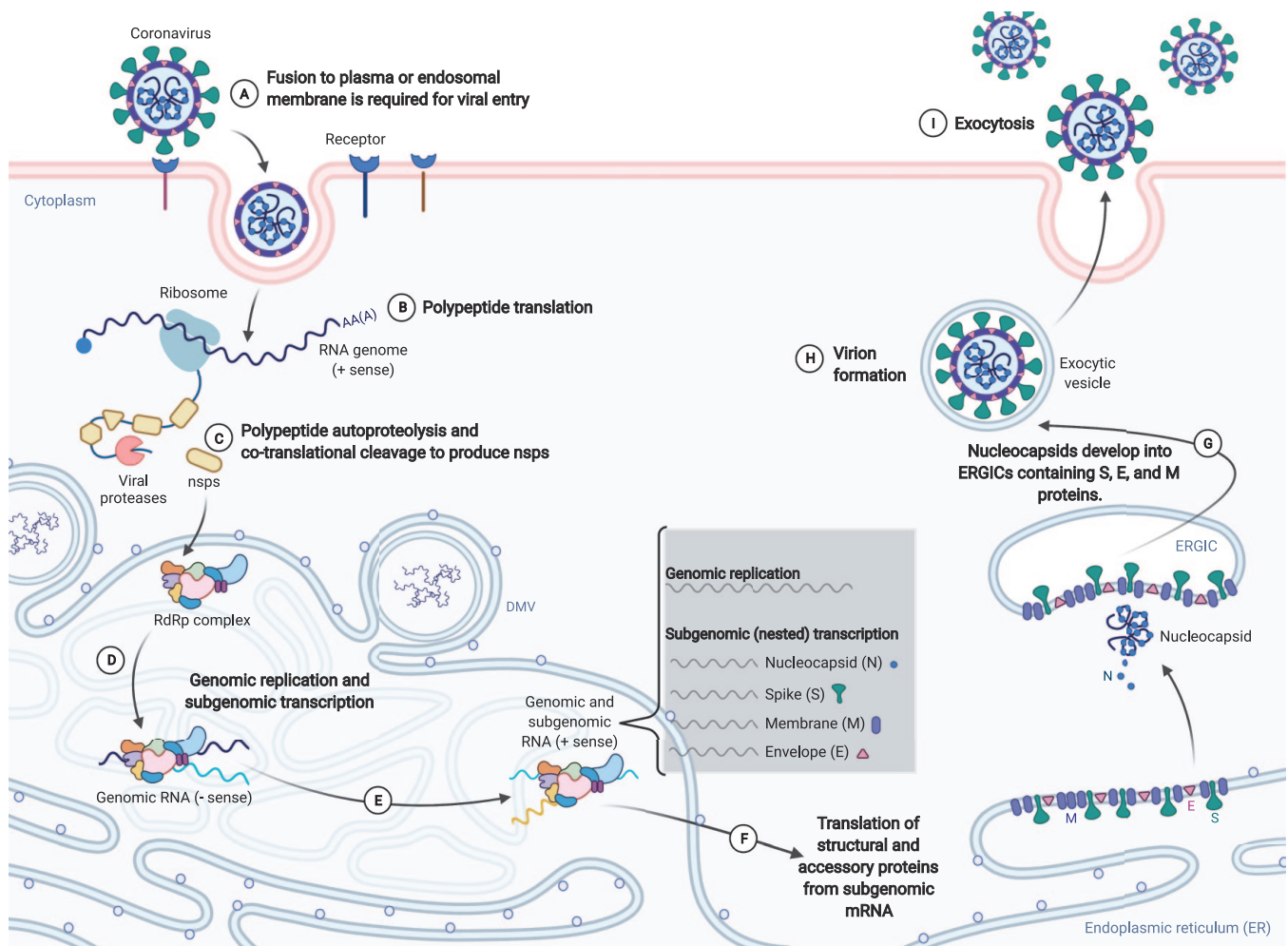
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**Figure 1.** Structural features of SARS-CoV-2 and its main VOC. Key mutations in the S-glycoprotein are displayed for each VOC. Source: Adapted from 'The SARS-CoV-2 Variants of Concern' by BioRender.com.

polymerase (RdRp). Owing to their particular importance as druggable targets, these enzymes are described in further detail in the main body of the review. Another potential pharmacologic target is the S-glycoprotein, which has also been heavily investigated as the main target of antibodies, elicited by both natural infection and by

vaccination. This is the case for all the main vaccine platforms that have proven most successful so far, such as vaccines based on mRNA (BNT162b2 and Spikevax) or adenoviral vector vaccines (ChAdOx1-S and Ad26.COV2.S).<sup>7</sup> Therefore, the evolution of the S-glycoprotein remains closely monitored to track the



**Figure 2.** Schematic depiction of the SARS-CoV-2 life cycle. (A) SARS-CoV-2 binds to the surface receptor, angiotensin-converting enzyme 2 (ACE-2), on the host cell and releases its RNA genome in the cytoplasm *via* endocytosis or direct membrane fusion. (B) The host translation machinery translates the positive-sense viral genome. (C) This produces polyproteins that are co-translationally cleaved by proteases encoded in the polyprotein to produce the components of the viral RdRp complex. (D and E) The RdRp complex generates negative sense subgenomic and genome-length RNAs using the viral genome as a template. These are then employed as templates for the creation of full-length positive-sense progeny genomes and subgenomic mRNAs. (F) Structural and accessory proteins are translated from subgenomic mRNAs. (G) The structural proteins S, E and M, translated from positive-sense subgenomic RNAs, adorn the endoplasmic-reticulum-Golgi intermediate compartment (ERGIC), while the positive-sense genomic RNA is bound by the nucleocapsid. (H and I) A new virion is formed and released from the host cell by exocytosis. Source: Adapted from 'Coronavirus Replication Cycle' by BioRender.com (2020).

development of mutations that may favor immune evasion (Figure 1). In this regard, some of the so-called variants of concern (VOCs), that is, B.1.1.7 (alpha), B.1351 (beta), P.1 (gamma), B.1.617.2 (delta), and B.1.1.529 (omicron)<sup>8</sup> are already characterized by increased transmissibility and severity, or as compared with the original strain.<sup>9,10</sup> This, in turn, can partially explain the variable re-infection, hospitalization, and death rates observed during the multiple waves of infection.<sup>11</sup>

While the symptoms of SARS-CoV-2 infection, if present, vary greatly between individuals, the development of severe COVID-19 is usually accompanied by three stages: (a) early infection, which includes the various steps of viral replication (Figure 2) and is associated with mild symptoms; (b) pulmonary involvement, in which there is adaptive immunity stimulation and the predominance of respiratory symptoms; and (c) hyperinflammation, which is associated with immune dysregulation and often includes the Acute

Respiratory Distress Syndrome (ARDS). In addition, COVID-19 patients have been reported to display a circadian clinical course, with deterioration after initial improvement, which is consistent with a delayed and exaggerated immune activation.<sup>12,13</sup> This hyperactivation can lead to a ‘cytokine storm’, possibly accompanied by dysregulation of pulmonary macrophages, dendritic cells, and leading to ARDS in these patients.<sup>14</sup> In line with this, multiple inflammatory cytokines and chemokines [interleukin (IL)-1, IL-6, IL-7, IL-8, IL-9, IL-10, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN), interferon-gamma-induced protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1 (MIP-1)] are elevated in the blood of COVID-19 patients, especially those requiring admission to an intensive care unit (ICU).<sup>15,16</sup> Consequently, the hyperinflammatory response to COVID-19 shares biochemical similarities with the macrophage activation syndrome, implying that targeting the innate immune system could be a viable technique to reduce disease severity.<sup>17</sup>

Although the morbidity and mortality of the infection have been significantly reduced by the implementation of broad vaccination campaigns,<sup>18</sup> SARS-CoV-2 transmission is still ongoing leading to further hospitalizations and deaths. It is therefore generally accepted that effective therapies will be an indispensable complement to vaccination strategies. At present, only few drugs are approved at least in some countries for use against SARS-CoV-2 infection. These include antiviral formulations (molnupiravir, nirmatrelvir/ritonavir, remdesivir, several monoclonal antibodies) or medicaments to decrease immune hyperactivation (dexamethasone, tocilizumab, baricitinib) [sources: WHO <https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-therapeutics-2022.2>; United States Food and Drug Administration (FDA): <https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs>].

Notably, with the important exception of nirmatrelvir, the approved drugs in the list, as well as several drug candidates, were devised following a drug repurposing approach. In comparison with the *de novo* drug discovery process, drug repurposing is based on discovering new applications for licensed or investigational medications, thus

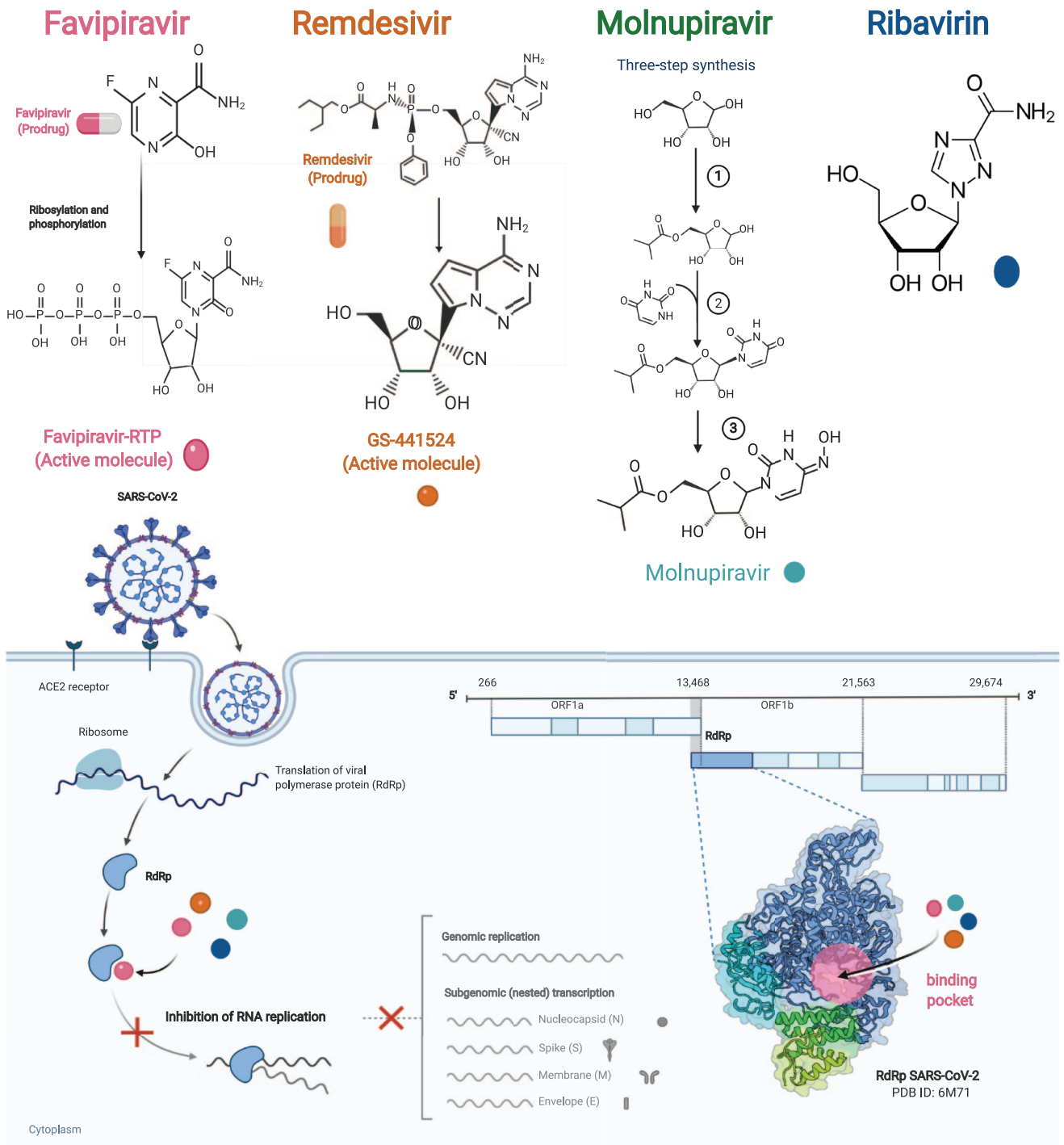
curtailing time, cost, and risk of side effects associated with the development of new chemical entities.<sup>19</sup> The scientific rationale of drug repurposing is supported by the observation that disease targets are frequently shared by a variety of pathogenic processes, thus facilitating the development of novel indications for drugs with a well characterized target.<sup>20</sup>

A plethora of repurposed drugs have been tested as the beginning of the SARS-CoV-2 outbreak, several of which had been already proposed during the earlier, and more contained, epidemics of SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).<sup>21</sup> Although the disappointing clinical results of some repurposed compounds have dampened the early hope that an effective therapy could be immediately devised, some drugs – such as molnupiravir, remdesivir, baricitinib, dexamethasone, and tocilizumab – have shown benefit in some late stage randomized clinical trials. These drugs have so far been mostly tested in monotherapy, although previous experience with RNA viruses, or retroviruses, such as hepatitis C virus (HCV)<sup>22</sup> or human immunodeficiency virus (HIV),<sup>23</sup> respectively, suggests that a potent combination therapy might be required to reproducibly decrease morbidity and mortality over time.

The current review provides an up-to-date outline of the most relevant repurposing attempts against SARS-CoV-2/COVID-19, including information on their mechanisms of action, pharmacokinetics, safety as well as their most relevant preclinical and clinical results. Moreover, the potential future developments in drug repurposing against SARS-CoV-2 are discussed, with particular focus on the possibility of combining effective compounds in a potent cocktail of antiviral and immune-modulating compounds.

### **Antivirals**

Drugs that inhibit key steps of the viral life cycle are generally regarded as the most straightforward and least toxic option to counteract acute viral infections. Their use is often more effective during the early stages of the infection, but they can be considered for later stages as well, if residual viral replication is suspected to fuel persistent inflammation. Some of the antiviral drugs repurposed for SARS-CoV-2 treatment act through



**Figure 3.** Summary and mechanism of action of the RdRp inhibitors described in the review.  
Source: Adapted from 'Favipiravir: Potential Repurposed Drug Candidate for COVID-19' by BioRender.com (2020).

direct inhibition of the activity of key viral enzymes, including two of the most successful repurposing attempts so far (molnupiravir and remdesivir) (Figure 3), while others modulate

some cellular factors necessary for viral replication. The sections below describe in detail the rationale and results of the most relevant antivirals tested so far against SARS-CoV-2.

### Molnupiravir

Molnupiravir (also known as EIDD-2801 and MK-4482, commercial name: Lagevrio) is an orally available prodrug that inhibits RNA viral replication (Figure 3) by inducing catastrophic mutations during transcription by the viral RdRp.<sup>24</sup> The drug was initially developed by Emory University's Drug Innovation Ventures for treatment of influenza.<sup>25</sup> while Merck and Ridgeback Biotherapeutics spearheaded the attempts to repurpose it for the prevention and treatment of COVID-19. *In vivo*, molnupiravir is rapidly converted to the ribonucleoside analogue  $\beta$ -D-N4-hydroxycytidine (NHC) by the host's esterases in plasma. NHC is then phosphorylated into its pharmacologically active ribonucleoside triphosphate (NHC-TP) after intracellular uptake. Finally, the incorporation of NHC-TP into viral RNA by the RdRp causes an accumulation of errors in the viral genome that eventually leads to replication inhibition.<sup>26</sup> This mechanism of action has raised some concerns about the possible mutagenicity and teratogenicity of molnupiravir (<https://www.science.org/content/blog-post/rethinking-molnupiravir>), which have led to the exclusion of pregnant women from clinical trials. Of note, molnupiravir has shown broad-spectrum preclinical activity against all the main SARS-CoV-2 VOC.<sup>27</sup> Moreover, its oral route of administration facilitates its use in the early stages of the infection, improving scalability, as compared with other RdRp inhibitors such as remdesivir.<sup>28</sup> Recently, a phase III double-blind, randomized, placebo-controlled trial showed that an early treatment consisting of a 5-day course of 800mg molnupiravir every 12h was able to decrease the risk of hospitalization or death in SARS-CoV-2-infected patients.<sup>29</sup> Building on these results, molnupiravir was approved for the first time in the United Kingdom on 4 November 2021, for the treatment of mild-to-moderate COVID-19 in adults with at least one risk factor for severe illness.<sup>28</sup> Although the drug has also been approved by the FDA for emergency use, other countries, such as France, have been more cautious, citing concerns about its efficacy. Currently, several randomized, placebo-controlled clinical trials and real-world studies are assessing the safety and efficacy of molnupiravir, in preventing hospitalization, decreasing COVID-19 severity (END-COVID; NCT04405739)<sup>28</sup> and reducing spread of the infection within households (MOVE-AHEAD; NCT04939428). These trials will allow to define more robustly the potential of molnupiravir in treatment or prevention of COVID-19.

### Remdesivir

Remdesivir (GS-5734, commercialized as Veklury) is a 1'-cyano-substituted adenosine nucleotide analogue prodrug, and broad-spectrum antiviral with potential activity against a variety of RNA viruses.<sup>30</sup> Remdesivir acts by inhibiting the viral RdRp (Figure 3) and had been initially tested against Ebola Virus infection, without clinical success.<sup>31</sup> Remdesivir is in turn a derivative of the GS-441524 nucleoside analogue, which is used for treating feline infectious peritonitis caused by infection with feline coronavirus.<sup>32</sup> The intracellular delivery of GS-441524 and remdesivir is enhanced by the Pro-Tide technology.<sup>33</sup> Moreover, the conversion of remdesivir to an active metabolite, as with molnupiravir and other nucleoside analogues requires intracellular phosphorylation. In line with this, the addition of a monophosphate prodrug to the nucleoside dramatically increased its intracellular transport and activation<sup>34</sup> and was one of the significant achievements that allowed the development of this drug.

In terms of efficacy, it has been demonstrated that remdesivir potently reduces SARS-CoV-2 replication *in vitro*, and, to a lesser extent, *in vivo*.<sup>35</sup> Three coronavirus RdRp complexes (MERS-CoV, SARS-CoV, and SARS-CoV-2) share a specific termination site at the position I + 3 when treated with remdesivir, which implies that viral RNA synthesis stops after three more nucleotides are added, a process known as delayed chain-termination. While higher concentrations of the natural nucleotide pool can overcome RdRp-mediated termination, remdesivir typically shows a submicromolar EC<sub>50</sub> *in vitro* and a high selectivity index (SI > 129.87).<sup>35</sup>

The clinical results of remdesivir have been mixed. On one hand, remdesivir was the first FDA-approved medicine (<https://www.fda.gov/media/137564/download>.) for treating hospitalized COVID-19 patients. This was based on a preliminary report from a randomized, double-blind, placebo-controlled study enrolling 1062 hospitalized patients with COVID-19. The study showed that time to recovery and respiratory tract infections were significantly lower in treated patients.<sup>36</sup> On the other hand, subsequent reports failed to highlight a significant effect of remdesivir for moderate or severe COVID-19,<sup>37,38</sup> including the interim analysis of the WHO Solidarity trial, which included 2750 patients.<sup>39</sup> More recently, however, an early three-day course of remdesivir in patients with

mild/moderate COVID-19 was shown to decrease the likelihood of hospitalization and death.<sup>40</sup>

Despite these promising results, the widespread early adoption of remdesivir might be impaired by its administration route (parenteral), which limits its use outside hospital settings, and by its suboptimal *in vivo* absorption, which might explain the partially reduced efficacy as compared with *in vitro* effects.<sup>41</sup> Several options are under investigation to overcome these limitations including novel oral formulations of the drug,<sup>42</sup> the use of its parent drug GS-441524<sup>43</sup> which displays a better oral availability.

### Favipiravir

Favipiravir (T-705, commercialized as FabiFlu) is a purine nucleic acid analogue which can inhibit the RdRp (Figure 3) of several RNA viruses, including norovirus, Ebola virus, and influenza virus.<sup>44</sup> Favipiravir was approved for treatment of influenza virus in Japan in 2014.

Inside cells, favipiravir is converted to an active phosphoribosylated form [favipiravir-ribofuranosyl-5' triphosphate (RTP)], which is recognized as a substrate by the RdRp, inhibiting its activity, including that of SARS-CoV-2 (Figure 3).<sup>45</sup> The recommended therapeutic dose of favipiravir, according to the Japanese Association for Infectious Diseases, is 1800mg twice a day on day 1, then 800mg twice a day for 7 days, with the possibility of continuing for up to 14 days if needed.<sup>46</sup> Multiple clinical trials testing favipiravir in patients with COVID-19 have been conducted so far, with some, including an open-label phase III study, suggesting that favipiravir might accelerate recovery time,<sup>47</sup> disappearance of symptoms,<sup>48</sup> and viral clearance.<sup>49</sup> Mixed effects, however, were obtained when analyzing time to reverse transcription polymerase chain reaction (RT-PCR) negativization, and other trials did not observe any statistical benefit,<sup>50,51</sup> or only moderate benefit on symptoms such as pyrexia and cough.<sup>52</sup>

The overall quality of evidence for favipiravir is still low, with few randomized placebo-controlled trials published so far. Recent meta-analyses have attempted to quantify a potential benefit of favipiravir based on the clinical evidence accumulated so far. These analyses could not highlight an improvement in mortality rate or mechanical ventilation,<sup>53,54</sup> but left open the possibility that

favipiravir might facilitate viral clearance and prevent hospitalization in patients with mild or moderate COVID-19.<sup>54</sup>

### Ribavirin

Ribavirin (RBV) (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, commercialized as Virazole®) is a typical choice of first use upon sudden outbreaks of emerging RNA virus infections. Before the SARS-CoV-2 pandemic, RBV had been tested to treat infections caused by a variety of viruses, including influenza, Lassa fever, Hantaan virus, and HCV infection.<sup>55</sup> RBV is a guanosine nucleoside analogue with structural similarities to other purines such as inosine and adenosine. RBV is thought to exert its antiviral effect through the exhaustion of the intracellular guanosine triphosphate (GTP) pool, thus inhibiting RdRp activity (Figure 3), or through disruption of viral mRNA capping.<sup>56</sup> Apart from this, RBV might influence adaptive immunity by altering CD4<sup>+</sup> T-cell responses toward a Th1 profile, an effect supported by RBV-mediated inhibition of IL-10 production by T-regulatory (Tregs), resulting in increased efficiency of CD4<sup>+</sup> T-cell effectors secreting IFN-γ.<sup>57</sup> *In vivo*, RBV has a 52% oral bioavailability<sup>58</sup> and only moderate liver first-pass metabolism. Although RBV was approved by the FDA in 1986 as an aerosol for new-borns with the respiratory syncytial virus,<sup>59</sup> the clinical benefit associated with its use against RNA viruses is generally weak or absent. In line with this, RBV's antiviral efficacy against SARS-CoV is modest *in vitro* (EC50 of 109.50 μM in Vero cells),<sup>34</sup> and its addition to supportive care was not associated with clinical improvement in severe SARS-CoV-2 patients.<sup>60</sup> For these reasons, RBV has been tested mostly in combination with other antiviral or immune-modulating drugs, also in this case with modest results, as described below in the section dedicated to drug combinations.

### Lopinavir/ritonavir

Lopinavir was suggested, along with other HIV protease inhibitors, such as darunavir, as a candidate drug to target the main protease (MPro) of SARS-CoV-2. In particular, lopinavir was tested in its common co-formulation (marketed as Kaletra) with the cytochrome P450 3A (CYP3A) inhibitor ritonavir. Ritonavir is known to increase the activity of several protease inhibitors<sup>61</sup> by decreasing liver first-pass metabolism.<sup>61</sup> Interestingly, during



the SARS-CoV epidemic in 2003, lopinavir had been shown to inhibit the main protease of the virus *in vitro*, and *in silico* studies clarified the basis for this interaction.<sup>62</sup> These promising results supported its early testing during the SARS-CoV-2 pandemic, in light of the evolutionary conservation of the enzyme.<sup>63</sup> On the contrary, the use of lopinavir/ritonavir has brought mostly disappointing results in clinical trials of SARS-CoV-2 patients. In a trial at the University of Hong Kong, testing several possible combinations, the ritonavir/lopinavir group alone was not different from standard of care in hospitalized patients with severe COVID-19.<sup>64</sup> Similar results were obtained in the SOLIDARITY and the TOGETHER trials,<sup>65</sup> and have led the World Health Organization (WHO) to announce that the use of lopinavir/ritonavir for treatment of hospitalized patients would be discontinued (<https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19>).

#### *Chloroquine and hydroxychloroquine*

Apart from malaria, chloroquine (CQ) and hydroxychloroquine (HCQ) are approved by the FDA for treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.<sup>66</sup> The repurposing of CQ and HCQ as antivirals has been proposed mainly based on their ability to impair endosomal acidification, which is required for the activation of endosomal proteases responsible for the initiation of virus/endosome fusion.<sup>66</sup>

Although during the early stages of the pandemic, CQ/HCQ were shown to impair SARS-CoV-2 replication *in vitro*<sup>35</sup> both previous and more recent pharmacodynamic considerations indicated that the drugs were unlikely to reach the required intracellular concentrations to match the antiviral activity observed *in vitro* (i.e. low micromolar EC50).<sup>67,68</sup> Interestingly, the history of CQ repurposing in COVID-19 mirrors its previous failure to treat HIV/AIDS, which was predicted based on similar pharmacokinetic considerations.<sup>67,68</sup> In line with this, clinical results have been disappointing.<sup>65,69–74</sup>

#### *Amodiaquine*

Amodiaquine (AQ), is like, CQ/HCQ, another anti-malarial derivative of the quinoline class of chemicals. AQ was proposed as a compound with a

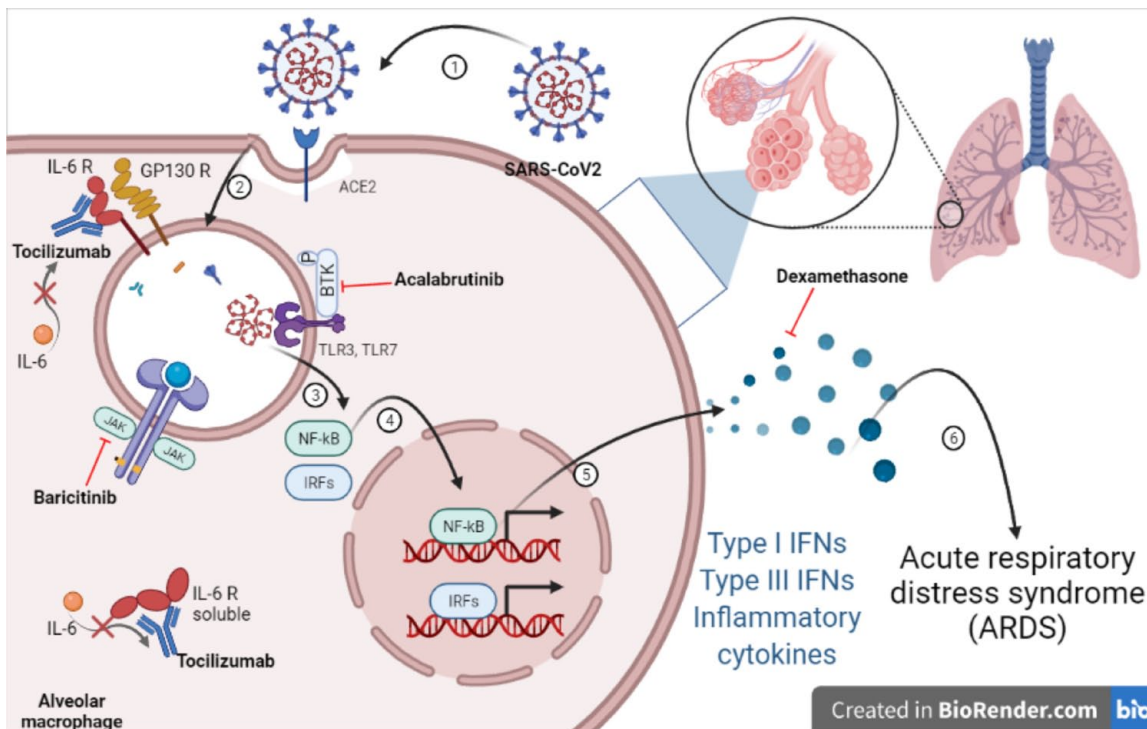
similarly pleiotropic, but more potent, antiviral activity as compared with CQ/HCQ.<sup>75</sup> *In vivo*, AQ is rapidly converted into its active metabolite, desethylamodiaquine, which has a significantly longer half-life (about 9–18 days *versus* 5 h for AQ) when given to humans.<sup>76</sup> When tested in a model of human bronchial-airway-on-a-chip desethylamodiaquine could decrease by 60% the entry of pseudotyped SARS-CoV-2 viral particles.<sup>77</sup> Moreover, subcutaneous prophylactic administration of AQ in hamsters, at a dose of 50 mg/kg, led to a significant reduction of SARS-CoV-2 viral load.<sup>78</sup> Despite these promising results, clinical data of AQ in COVID-19 patients are still lacking and the experience with CQ/HCQ suggests that achieving effective drug concentrations in humans, especially upon oral administration, might be challenging.

#### *Ivermectin*

Ivermectin is a widely used antiparasitic medication that is approved by the FDA for both veterinary and human medicine.<sup>79</sup> The repurposing of ivermectin for SARS-CoV-2 use was proposed due to the well-established broad antiviral activity of this drug *in vitro*. This activity is likely mediated by the inhibition of viral protein nuclear import mediated by importin  $\alpha/\beta$ .<sup>80</sup> Ivermectin was previously shown to inhibit *in vitro* the replication of a wide range of viruses, including HIV, dengue fever, influenza, and Zika virus, and more recently, SARS-CoV-2.<sup>81</sup> In addition, ivermectin was proposed to have an immunomodulatory effect, exerted on T-lymphocyte function and counts,<sup>82</sup> and to decrease the production of various cytokines, including tumor necrosis factor alpha (TNF- $\alpha$ ), IL-1ss, IL-6, IL-4, IL-13, and IL-5.<sup>83</sup> Indeed, the immune-modulating, rather than the antiviral, effect was proposed as the primary driver of clinical improvement in SARS-CoV-2-infected hamsters.<sup>84</sup> As a result, ivermectin was postulated to play a role against the development of the ‘cytokine storm’ characteristic of severe COVID-19. Despite these lines of evidence and some scattered clinical reports suggesting a benefit of the drug *in vivo*, however, randomized clinical trials have failed to show any significant effect of the drug as postexposure prophylaxis or in treating mild infections or preventing hospitalizations.<sup>85–90</sup>

#### **Immune modulators**

The severity of COVID-19 is determined largely by a dysregulated immune response, potentially



**Figure 4.** Inhibition of SARS-CoV-2-mediated cytokine storm by immune-modulating drugs. A hyperinflammatory response or ‘cytokine storm’ has been proposed as a significant pathogenetic contributor and as a cause of ARDS in COVID-19 patients. Toll-like receptors (TLRs) in macrophages recognize ssRNA from viruses such as SARS-CoV-2 and activate nuclear factor B (NF-κB) signaling, *via* BTK-dependent activation, as well as other pro-inflammatory pathways (JAK/STAT), resulting in the production of a variety of inflammatory chemokines and cytokines (e.g. IL-6). Anti-inflammatory drugs – including dexamethasone, acalabrutinib, baricitinib, and tocilizumab (TCZ) – inhibit the activation of pro-inflammatory cytokines at different steps, as shown in the figure. Source: Created with BioRender.com.

leading to a cytokine storm and damage to multiple organs.<sup>91</sup> It is not surprising, therefore, that many of the drug repurposing approaches have focused on compounds able to decrease immune hyperactivation (Figure 4). Although some broad-spectrum weak antivirals, such as CQ/HCQ and ivermectin, can also play a role in immune function, the following sections will detail only the most popular approaches specifically focused on drugs whose primary or only role is immunomodulatory.

### Dexamethasone

Dexamethasone is a synthetic corticosteroid immunosuppressant that is widely used to reduce inflammation and immune responses in a plethora of conditions, particularly autoimmune, respiratory, and severe allergic syndromes.<sup>92</sup> Owing to its low cost and high potency, dexamethasone was quickly proposed to treat COVID-19 patients

and was the first drug to show a significant benefit in the large RECOVERY trial.<sup>93</sup> Specifically, this trial demonstrated that a moderate dose of dexamethasone (6 mg daily for 10 days intravenous administration) can decrease mortality in hospitalized patients with COVID-19 and respiratory failure who required supplemental oxygen or mechanical ventilation.<sup>94</sup>

A subsequent trial further demonstrated that intravenous dexamethasone plus standard of care, compared with standard of care alone, resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days in patients with moderate COVID-19 or ARDS.<sup>95</sup> Moreover, also a short course of dexamethasone was demonstrated to decrease inflammation levels (as shown by lower C-reactive protein levels) and accelerate recovery time.<sup>96</sup>

Based on this evidence, dexamethasone (and corticosteroids in general) were the first drugs recommended by the WHO, in November 2020, for the treatment of severe or critical COVID-19 (COVID-19: living guideline WHO). Dexamethasone is now routinely used to manage the cytokine storm and hyperinflammation in COVID-19 patients, and it is also recommended as a treatment for immune thrombocytopenic purpura caused by COVID-19.<sup>97</sup>

#### *Tocilizumab*

Tocilizumab (TCZ, commercialized as Actemra) is a humanized monoclonal antibody (mAb) that belongs to the immunoglobulin G1K subclass and binds to the soluble and membrane-bound interleukin-6 receptor (IL-6R)<sup>98</sup> (Figure 4). The repurposing of TCZ was driven by its well-known clinical efficacy, pharmacokinetics and favorable safety profile for treatment of rheumatoid arthritis.<sup>99</sup> Apart from rheumatoid arthritis, TCZ is also used to treat cytokine release syndrome/systemic inflammatory response syndrome that can occur as a side effect of cancer immunotherapy<sup>100</sup> or chimeric antigen receptor (CAR)-T therapy.<sup>101</sup> Importantly, IL-6 levels have been linked to ARDS severity and outcome in COVID-19 patients.<sup>102</sup> In line with this, TCZ has been recommended as an effective treatment for hospitalized COVID-19 patients, especially for those who display high levels of circulating IL-6.<sup>103</sup>

In a study conducted in China during the early stages of the pandemic, TCZ treatment improved oxygen intake, lung lesion opacity and lymphocyte counts, and decreased the inflammatory marker C-reactive protein.<sup>104</sup> All patients were discharged on average 15.1 days after receiving TCZ.<sup>104</sup> Moreover, another open-label, noncontrolled trial conducted in China showed that a single intravenous dose of 400 mg TCZ can be effective in COVID-19 patients with mild-to-moderate ARDS.<sup>105</sup> On the contrary, placebo-controlled phase III studies showed mixed results of TCZ in hospitalized patients with severe COVID-19 pneumonia.<sup>106,107</sup> Heterogeneous results were also observed in other randomized trials.<sup>108–114</sup> Despite these mixed results, recent meta-analyses suggest that TCZ use might be associated with lower mortality,<sup>115</sup> and the WHO has recommended its use in COVID-19 patients (COVID-19: living guideline WHO).

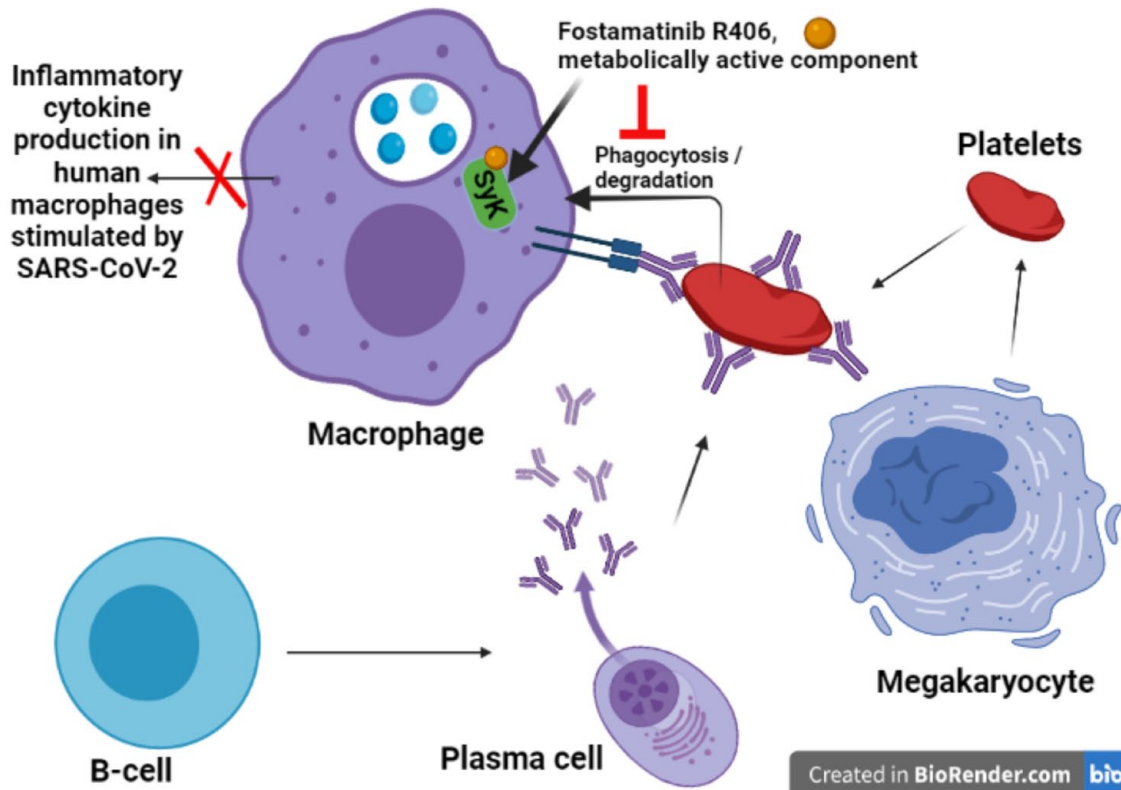
#### *Baricitinib*

Baricitinib (commercial name: Olumiant) is an anti-inflammatory drug that is approved for treatment of rheumatoid arthritis.<sup>116</sup> At the molecular level, baricitinib acts as a selective inhibitor of the Janus kinase 1 and 2 (JAK 1/2) (Figure 4) at nanomolar concentrations.<sup>117</sup> Through its inhibitions of JAKs, baricitinib impairs the downstream activation of signal transducers and activators of transcription (STATs), thus impairing their nuclear translocation and the response of immune cells to pro-inflammatory cytokine secretion.<sup>118</sup> Owing to its anti-inflammatory effect, favorable route of administration (oral), and safety,<sup>119</sup> baricitinib was proposed as a therapeutic candidate for COVID-19. After proving effective in resolving lung inflammation in SARS-CoV-2-infected rhesus macaques,<sup>120</sup> baricitinib, plus standard of care, proved able to reduce mortality of hospitalized COVID-19 patients in a randomized placebo-controlled phase III clinical trial.<sup>121</sup> Recently, in January 2022, the WHO has included baricitinib as one of the recommended therapeutic options for treatment of severe COVID-19, a list previously including corticosteroids and TCZ (COVID-19: living guideline WHO).

#### *Acalabrutinib*

Acalabrutinib (also known as ACP-196, marketed as Calquence) is an irreversible covalent inhibitor of Bruton's tyrosine kinase (BTK) (Figure 4). Three BTK inhibitors – ibrutinib, zanubrutinib, and acalabrutinib – are approved by the FDA to treat B-cell malignancies such as chronic lymphocytic leukemia and mantle B-cell lymphoma.<sup>122</sup> Acalabrutinib is a second generation BTK inhibitor and is characterized by better oral absorption, higher selectivity, and lower adverse effects, as compared with ibrutinib.<sup>122,123</sup> Interestingly, before the outbreak of SARS-CoV-2, BTK inhibitors have been shown to protect against severe lung injury in preclinical research.<sup>124,125</sup>

At the molecular level, BTK inhibition might mitigate COVID-19 by decreasing macrophage activation. Macrophages contribute to the COVID-19 inflammatory response through phagocytic absorption of viral particles or cellular debris harboring viral ssRNA. Using double-stranded areas in its secondary structure, the viral ssRNA can bind to TLR7 and TLR8, as well as TLR3, thus



**Figure 5.** Activity of fostamatinib in decreasing thrombocytopenia. The metabolically active component of fostamatinib, R406, inhibits the enzyme spleen tyrosine kinase (SYK). This prevents the destruction of platelets induced by the SYK-dependent cytoskeletal reorganization during phagocytosis. Source: Created with BioRender.com.

recruiting and activating BTK.<sup>126</sup> BTK in turn can activate NF- $\kappa$ B signaling, leading to the generation of pro-inflammatory cytokines and chemokines and potentially to a cytokine storm by boosting monocyte/macrophage and neutrophil recruitment during the late stages of severe COVID-19 infection<sup>127</sup> (Figure 4).

Early data on the off-label clinical use of acalabrutinib showed improved oxygenation, normalization of IL-6 levels, and reduction of lymphopenia in patients with severe COVID-19.<sup>128</sup> In this small study, 8/11 treated patients in the supplementary oxygen cohort could be discharged on room air and 4/8 patients in the mechanical ventilation cohort could successfully undergo extubation.<sup>128</sup> Unfortunately, in subsequent phase II randomized trials (CALAVI program, NCT identifiers: NCT04380688 and NCT04346199), acalabrutinib did not decrease mortality and respiratory failure (<https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-calavi-phase-ii-trials-for-calquence-in->

[patients-hospitalised-with-respiratory-symptoms-of-covid-19.html](https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-calavi-phase-ii-trials-for-calquence-in-patients-hospitalised-with-respiratory-symptoms-of-covid-19.html)). Therefore, the use of acalabrutinib, as well as that of other BTK inhibitors, is currently not recommended for treatment of COVID-19.

#### *Fostamatinib*

Severe COVID-19 is often associated with thrombocytopenia.<sup>129</sup> Fostamatinib (marketed as Tavalisse or Tavlesse) is an FDA-approved inhibitor of the spleen tyrosine kinase (SYK) and is typically used to prevent chronic immune-mediated destruction of platelets.<sup>130</sup> In several immune cells, such as, neutrophils, platelets, monocytes, and macrophages, SYK signaling occurs *via* Fc receptors or c-type lectin receptors.<sup>131</sup> By inhibiting FcRIIA receptor-mediated SYK signaling, the active metabolite of fostamatinib (R406) has been shown to reduce inflammatory cytokine production in human macrophages stimulated by COVID-19 plasma<sup>132</sup> (Figure 5). Interestingly, Kost-Alimova *et al.*<sup>133</sup> reported that fostamatinib can also drastically

reduce Mucin-1 (MUC1) protein abundance. MUC1 is a member of the mucin family of proteins and is responsible for the production of protective mucus on the epithelial apical membrane of several tissues, including lungs.<sup>134</sup> The overexpression of MUC1 has been observed in COVID-19 patients,<sup>135</sup> potentially explaining the excessive mucus production in the airways of COVID-19 patients displaying symptoms of ARDS. Therefore, fostamatinib might mitigate COVID-19 progression through a dual effect, by reducing both thrombocytopenia and excessive airway epithelium mucus production.

In line with this, a randomized placebo-controlled trial of fostamatinib, plus standard of care, was associated with lower mortality and faster recovery in hospitalized COVID-19 patients.<sup>136</sup> Despite these promising results, the number of enrolled patients was small, and definitive evidence of the efficacy of fostamatinib is still lacking. An ongoing phase III clinical trial is expected to provide additional data on the potential of fostamatinib in treating COVID-19.<sup>137</sup>

### Drug combinations

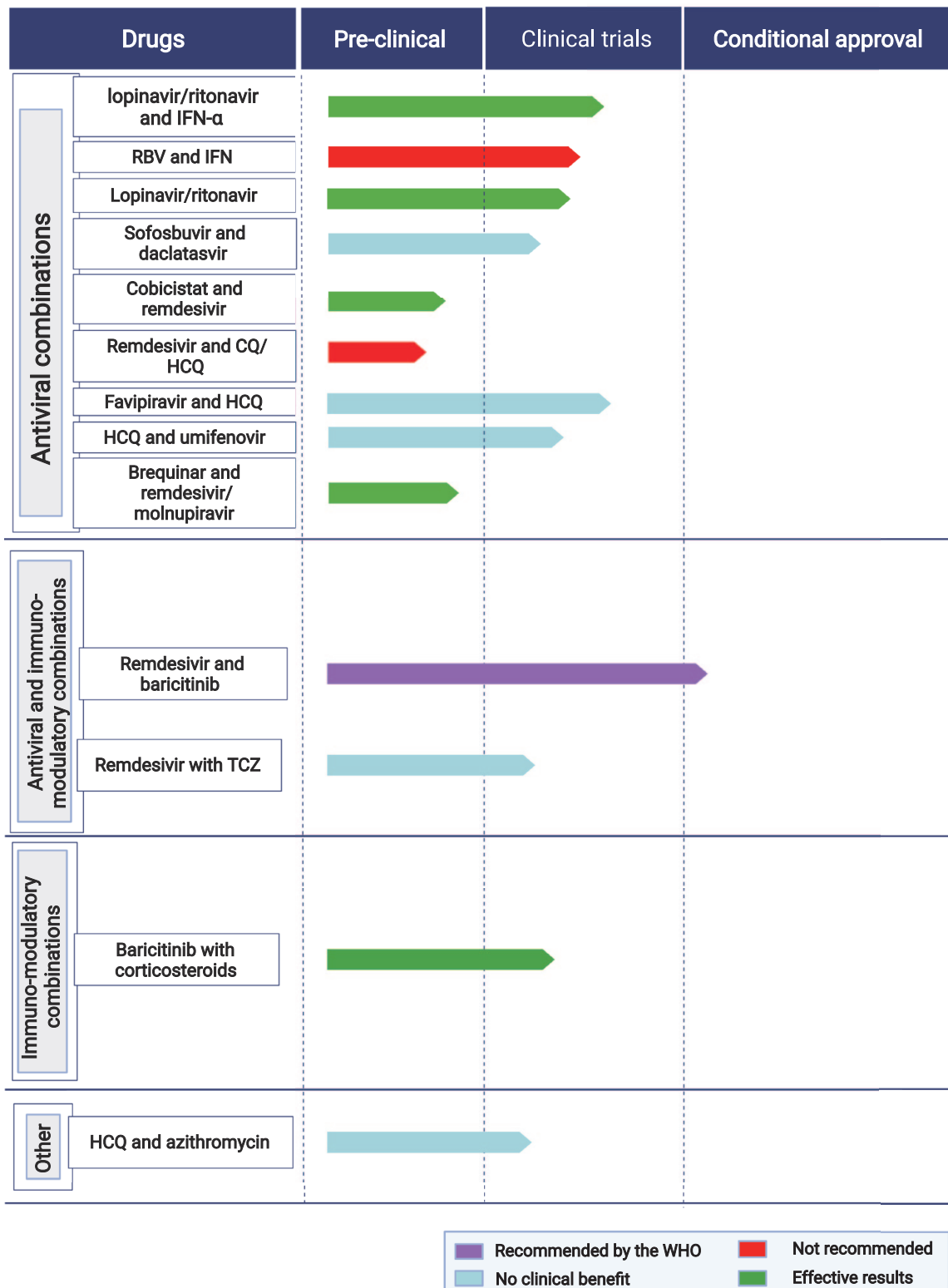
Combining effective, or partially effective compounds might provide several advantages over monotherapies. Combinations of antivirals could increase the barrier to resistance mutations and extend the time window in which treatment is effective, potentially leading to full suppression of viral replication. Previous experience with other RNA viruses<sup>22</sup> or retroviruses<sup>138</sup> suggests that a combination of two/three antivirals might be required to achieve reproducible results in wide patient cohorts and across different viral subtypes/variants. On the contrary, only sporadic cases of drug resistance mutations have been observed so far in SARS-CoV-2,<sup>139</sup> possibly due to the short period of administration or of evolutionary constraints of the viral enzymes targeted. Moreover, data on drug–drug interaction and efficacy of antiviral combinations in SARS-CoV-2-infected patients are still scarce.<sup>140</sup> Initial guidelines recommended avoiding the combination of remdesivir and CQ/HCQ, due to potential toxicity. In addition, combining favipiravir and HCQ did not provide any clinical benefit in hospitalized patients with moderate-to-severe COVID-19.<sup>141</sup> Similarly disappointing results were obtained by combining HCQ and the antibiotic azithromycin.<sup>142</sup> On the contrary, a combination of lopinavir/ritonavir and IFN- $\beta$ 1b showed more effective than single

treatments in an open-label, randomized, phase II trial enrolling hospitalized adults with mild or moderate COVID-19.<sup>143</sup>

Encouraging results were also obtained by associating lopinavir/ritonavir and IFN- $\alpha$  with RBV.<sup>30</sup> In another trial, however, the combination of RBV and IFN did not appear to improve clinical results in COVID-19 patients.<sup>144</sup> Indeed, current guidelines indicate that the combination of RBV and IFN should be avoided in patients with COVID-19 (National Institute of Health, 2020; WHO, 2021b). More generally, the evidence of the benefit of combination treatments including IFN for SARS-CoV-2 patients is limited, and the use of IFN can be associated with significant toxicities.<sup>145</sup> Also attempts to further increase the efficacy of the combination by adding HCQ and umifenovir (i.e. another repurposed drug used to inhibit fusion of RNA viruses)<sup>146</sup> were not successful.<sup>147</sup> Similarly unsuccessful was the attempt to potentiate the effect of RBV by repurposing the direct acting antivirals sofosbuvir and daclatasvir, which are typically used to HCV infection.<sup>148</sup> Despite this, other trials suggest that combining sofosbuvir and daclatasvir with a standard of care including other repurposed compounds – such as HCQ, remdesivir, ivermectin, or lopinavir/ritonavir – might have a marginal benefit.<sup>149,150</sup> The evidence is, however, still insufficient to support the addition of sofosbuvir and daclatasvir to antiviral combinations for treating COVID-19 patients.

Overall, clinical data on purely antiviral combinations have been underwhelming so far. Some recent lines of preclinical evidence suggest that other repurposed compounds in the pipeline might help to fill this gap. In this regard, a recent study showed that the use of pyrimidine biosynthesis inhibitors, such as brequinar, can significantly potentiate the effect of the RdRp inhibitors remdesivir and molnupiravir in a mouse model of SARS-CoV-2 infection.<sup>151</sup> Although brequinar is not approved by the FDA and can be associated with high toxicity,<sup>152</sup> the dose used in the study was well tolerated and effective.

In another study, conducted by some of us, the CYP3A inhibitors cobicistat was shown to decrease viral replication and disease progression in a Syrian hamster model of SARS-CoV-2 infection, as well as to increase the potency of remdesivir.<sup>153</sup> The doses of cobicistat required to achieve an antiviral effect were higher than those employed to boost



**Figure 6.** Mechanism of action, effectiveness, and stage of development of the drug combinations described in the review. Color codes and bar lengths indicate, respectively, the available results/approval status and stage of development of each drug combination.

Source: Created with BioRender.com.

the effect of HIV protease inhibitors in antiretroviral therapy, thus potentially explaining lack of effect of the lower doses that had been observed in the early phases of the pandemic, when SARS-CoV-2 patients received cobicistat with darunavir in the standard formulation.<sup>154</sup> Of note, although this *in vitro* and *in vivo* study tested only the combination of cobicistat and remdesivir, more than 50% of all drugs are metabolized by the main cellular target of cobicistat (CYP3A),<sup>155</sup> thus potentially paving the way to the design of multidrug combinations in which cobicistat could play a dual role as antiviral and pharmacoenhancer.

Other approaches at drug combinations, typically used in more advanced stages of COVID-19, include associating antivirals and immune-modulating drugs or a cocktail of immune-modulating drugs. Most trials of this type have been conducted by associating remdesivir with immune modulators such as the TCZ or other monoclonal antibodies targeting pro-inflammatory pathways. None of these combinations, however, proved a significant clinical benefit in hospitalized patients with COVID-19<sup>156</sup> (<https://www.roche.com/media/releases/medcor-2021-03-11>). On the contrary, the combination of remdesivir and baricitinib accelerated clinical improvement in hospitalized COVID-19 patients as compared with remdesivir only.<sup>157</sup> These promising results led to the approval of Emergency Use Authorization of this drug combination by the FDA. Similarly, positive results were obtained in an observational clinical trial by testing the combination of baricitinib with corticosteroids, which led to improved pulmonary function.<sup>158</sup>

### Conclusion

The Herculean efforts in drug repurposing have led to the identification of several antiviral and immune-modulating compounds to treat SARS-CoV-2/COVID-19. Although many of the proposed compounds could not pass rigorous clinical scrutiny, a subset of drugs proved able to decrease the mortality and morbidity of the infection, thus confirming the potential of the drug repositioning approach as a fast-response framework to confront sudden viral outbreaks or novel epidemics. Despite their promise, drug combinations have so far yielded only sporadic or early-stage results (Figure 6). Research is ongoing on the optimal compounds/formulations that could allow to improve current treatments at both the early and the advanced infection stages.

### Declarations

*Ethics approval and consent to participate*  
Not applicable.

*Consent for publication*  
All authors agree.

### Author contributions

**Noha Samir Taibe:** Conceptualization; Data curation; Visualization; Writing – original draft.

**Maimona A. Kord:** Supervision.

**Mohamed Ahmed Badawy:** Supervision.

**Iart Luca Shytaj:** Supervision; Writing – review & editing.

**Mahmoud M. Elhefnawi:** Conceptualization; Supervision; Writing – review & editing.

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### Availability of data and materials

Not applicable.

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### References

1. Lythgoe MP and Middleton P. Ongoing clinical trials for the management of the COVID-19 pandemic. *Trends Pharmacol Sci* 2020; 41: 363–382.
2. Lu R, Zhao X, Li J, *et al.* Genomic characterisation and epidemiology of 2019 novel

- coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; 395: 565–574.
3. Manhas S, Anjali A, Mansoor S, *et al.* Covid-19 pandemic and current medical interventions. *Arch Med Res* 2020; 51: 473–481.
  4. Rothan HA and Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020; 109: 102433.
  5. Boson B, Legros V, Zhou B, *et al.* The SARS-CoV-2 envelope and membrane proteins modulate maturation and retention of the spike protein, allowing assembly of virus-like particles. *J Biol Chem* 2021; 296: 100111.
  6. Schoeman D and Fielding BC. Coronavirus envelope protein: current knowledge. *Virology* 2019; 16: 69.
  7. Molino D, Durier C, Radenne A, *et al.* A comparison of Sars-Cov-2 vaccine platforms: the CoviCompare project. *Nat Med* 2022; 28: 882–884.
  8. Bojkova D, Widera M, Ciesek S, *et al.* Reduced interferon antagonism but similar drug sensitivity in Omicron variant compared to Delta variant of SARS-CoV-2 isolates. *Cell Res* 2022; 32: 319–321.
  9. Escalera A, Gonzalez-Reiche AS, Aslam S, *et al.* Mutations in SARS-CoV-2 variants of concern link to increased spike cleavage and virus transmission. *Cell Host Microbe* 2022; 30: 373–387.e7.
  10. Stolp B, Stern M, Ambiel I, *et al.* SARS-CoV-2 variants of concern display enhanced intrinsic pathogenic properties and expanded organ tropism in mouse models. *Cell Rep* 2022; 38: 110387.
  11. Singhal T. The emergence of omicron: challenging times are here again! *Indian J Pediatr* 2022; 89: 490–496.
  12. Shi H, Han X, Jiang N, *et al.* Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; 20: 425–434.
  13. Shi Y, Wang Y, Shao C, *et al.* COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020; 27: 1451–1454.
  14. Channappanavar R, Fehr AR, Vijay R, *et al.* Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe* 2016; 19: 181–193.
  15. Luo P, Liu Y, Qiu L, *et al.* Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol* 2020; 92: 814–818.
  16. Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
  17. Bracaglia C, Prencipe G and De Benedetti F. Macrophage Activation Syndrome: different mechanisms leading to a one clinical syndrome. *Pediatr Rheumatol Online J* 2017; 15: 5.
  18. Watson OJ, Barnsley G, Toor J, *et al.* Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Inf Dis* 2022; 22: 1293–1302.
  19. Paolini GV, Shapland RH, van Hoorn WP, *et al.* Global mapping of pharmacological space. *Nat Biotechnol* 2006; 24: 805–815.
  20. Hodos RA, Kidd BA, Shameer K, *et al.* In silico methods for drug repurposing and pharmacology. *Wiley Interdiscip Rev Syst Biol Med* 2016; 8: 186–210.
  21. Dyllal J, Gross R, Kindrachuk J, *et al.* Middle east respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. *Drugs* 2017; 77: 1935–1966.
  22. Das D and Pandya M. Recent advancement of direct-acting antiviral agents (DAAs) in hepatitis C therapy. *Mini Rev Med Chem* 2018; 18: 584–596.
  23. Moreno S, Perno CF, Mallon PW, *et al.* Two-drug vs. three-drug combinations for HIV-1: do we have enough data to make the switch? *HIV Med* 2019; 20(Suppl. 4): 2–12.
  24. Malone B and Campbell EA. Molnupiravir: coding for catastrophe. *Nat Struct Mol Biol* 2021; 28: 706–708.
  25. Painter GR, Natchus MG, Cohen O, *et al.* Developing a direct acting, orally available antiviral agent in a pandemic: the evolution of molnupiravir as a potential treatment for COVID-19. *Curr Opin Virol* 2021; 50: 17–22.
  26. Lee CC, Hsieh CC and Ko WC. Molnupiravir – a novel oral anti-SARS-CoV-2 agent. *Antibiotics* 2021; 10: 1294.
  27. Abdelnabi R, Foo CS, De Jonghe S, *et al.* Molnupiravir inhibits replication of the emerging SARS-CoV-2 variants of concern in a hamster infection model. *J Infect Dis* 2021; 224: 749–753.
  28. Syed YY. Molnupiravir: first approval. *Drugs* 2022; 82: 455–460.
  29. Jayk Bernal A, Gomes da Silva MM, Musungaia DB, *et al.* Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *New Engl J Med* 2021; 386: 509–520.



30. Dong L, Hu S and Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther* 2020; 14: 58–60.
31. Mulangu S, Dodd LE, Davey RT, *et al.* A randomized, controlled trial of Ebola virus disease therapeutics. *New Engl J Med* 2019; 381: 2293–2303.
32. Pedersen NC, Perron M, Bannasch M, *et al.* Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis. *J Feline Med Surg* 2019; 21: 271–281.
33. McGuigan C, Hassan-Abdallah A, Srinivasan S, *et al.* Application of phosphoramidate ProTide technology significantly improves antiviral potency of carbocyclic adenosine derivatives. *J Med Chem* 2006; 49: 7215–7226.
34. Singh TU, Parida S, Lingaraju MC, *et al.* Drug repurposing approach to fight COVID-19. *Pharmacol Rep* 2020; 72: 1479–1508.
35. Wang M, Cao R, Zhang L, *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; 30: 269–271.
36. Beigel JH, Tomashek KM, Dodd LE, *et al.* Remdesivir for the treatment of Covid-19 – final report. *New Engl J Med* 2020; 383: 1813–1826.
37. Mahajan L and Singh AP. Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: a prospective randomised study. *Indian J Anaesth* 2021; 65(Suppl. 1): S41–S46.
38. Spinner CD, Gottlieb RL, Criner GJ, *et al.* Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA* 2020; 324: 1048–1057.
39. Repurposed antiviral drugs for covid-19 – interim WHO solidarity trial results. *New Engl J Med* 2020; 384: 497–511.
40. Gottlieb RL, Vaca CE, Paredes R, *et al.* Early remdesivir to prevent progression to severe covid-19 in outpatients. *New Engl J Med* 2021; 386: 305–315.
41. Hu WJ, Chang L, Yang Y, *et al.* Pharmacokinetics and tissue distribution of remdesivir and its metabolites nucleotide monophosphate, nucleotide triphosphate, and nucleoside in mice. *Acta Pharmacol Sin* 2021; 42: 1195–1200.
42. Xie Y, Yin W, Zhang Y, *et al.* Design and development of an oral remdesivir derivative VV116 against SARS-CoV-2. *Cell Res* 2021; 31: 1212–1214.
43. Cox RM, Wolf JD, Lieber CM, *et al.* Oral prodrug of remdesivir parent GS-441524 is efficacious against SARS-CoV-2 in ferrets. *Nature Commun* 2021; 12: 6415.
44. Qomara WF, Pramanissa DN, Amalia SH, *et al.* Effectiveness of remdesivir, lopinavir/ritonavir, and favipiravir for COVID-19 treatment: a systematic review. *Int J Gen Med* 2021; 14: 8557–8571.
45. Furuta Y, Komeno T and Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc Jpn Acad Ser B Phys Biol Sci* 2017; 93: 449–463.
46. Joshi S, Parkar J, Ansari A, *et al.* Role of favipiravir in the treatment of COVID-19. *Int J Infect Dis* 2021; 102: 501–508.
47. Udwardia ZF, Singh P, Barkate H, *et al.* Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. *Int J Infect Dis* 2021; 103: 62–71.
48. Doi Y, Hibino M, Hase R, *et al.* A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. *Antimicrob Agents Chemother* 2020; 64: e01897–20.
49. Cai Q, Yang M, Liu D, *et al.* Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering* 2020; 6: 1192–1198.
50. Lou Y, Liu L, Yao H, *et al.* Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. *Eur J Pharm Sci* 2021; 157: 105631.
51. Bosaeed M, Alharbi A, Mahmoud E, *et al.* Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicentre, placebo-controlled clinical trial. *Clin Microbiol Infect* 2022; 28: 602–608.
52. Chen C, Zhang Y, Huang J, *et al.* Favipiravir versus arbidol for clinical recovery rate in moderate and severe adult COVID-19 patients: a prospective, multicenter, open-label, randomized controlled clinical trial. *Front Pharmacol* 2021; 12: 683296.
53. Özlüßen B, Kozan Ş, Akcan RE, *et al.* Effectiveness of favipiravir in COVID-19: a live systematic review. *Eur J Clin Microbiol Infect Dis* 2021; 40: 2575–2583.

54. Deng W, Yang C, Yang S, *et al.* Evaluation of favipiravir in the treatment of COVID-19 based on the real-world. *Expert Rev Anti Infect Ther* 2022; 20: 555–565.
55. Yousefi H, Mashouri L, Okpechi SC, *et al.* Repurposing existing drugs for the treatment of COVID-19/SARS-CoV-2 infection: a review describing drug mechanisms of action. *Biochem Pharmacol* 2021; 183: 114296.
56. Cameron CE and Castro C. The mechanism of action of ribavirin: lethal mutagenesis of RNA virus genomes mediated by the viral RNA-dependent RNA polymerase. *Curr Opin Infect Dis* 2001; 14: 757–764.
57. Mondelli MU. The multifaceted functions of ribavirin: antiviral, immunomodulator, or both? *Hepatology* 2014; 60: 1126–1129.
58. Preston SL, Drusano GL, Glue P, *et al.* Pharmacokinetics and absolute bioavailability of ribavirin in healthy volunteers as determined by stable-isotope methodology. *Antimicrob Agents Chemother* 1999; 43: 2451–2456.
59. Patterson JL and Fernandez-Larsson R. Molecular mechanisms of action of ribavirin. *Rev Infect Dis* 1990; 12: 1139–1146.
60. Tong S, Su Y, Yu Y, *et al.* Ribavirin therapy for severe COVID-19: a retrospective cohort study. *Int J Antimicrob Agents* 2020; 56: 106114.
61. Chandwani A and Shuter J. Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. *Ther Clin Risk Manag* 2008; 4: 1023–1033.
62. Savarino A. Expanding the frontiers of existing antiviral drugs: possible effects of HIV-1 protease inhibitors against SARS and avian influenza. *J Clin Virol* 2005; 34: 170–178.
63. Nukoolkarn V, Lee VS, Malaisree M, *et al.* Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. *J Theor Biol* 2008; 254: 861–867.
64. Hung IF, Lung K-C, Tso EY-K, *et al.* Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020; 395: 1695–1704.
65. Reis G, dos Santos Moreira Silva EA, Silva DCM, *et al.* Effect of early treatment with hydroxychloroquine or lopinavir and ritonavir on risk of hospitalization among patients with COVID-19: the together randomized clinical trial. *JAMA Netw Open* 2021; 4: e216468.
66. Schrezenmeier E and Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol* 2020; 16: 155–166.
67. Savarino A and Shytaj IL. Chloroquine and beyond: exploring anti-rheumatic drugs to reduce immune hyperactivation in HIV/AIDS. *Retrovirology* 2015; 12: 51.
68. Tarek M and Savarino A. Pharmacokinetic basis of the hydroxychloroquine response in COVID-19: implications for therapy and prevention. *Eur J Drug Metab Pharmacokinet* 2020; 45: 715–723.
69. Barratt-Due A, Olsen IC, Nezvalova-Henriksen K, *et al.* Evaluation of the effects of remdesivir and hydroxychloroquine on viral clearance in COVID-19: a randomized trial. *Ann Intern Med* 2021; 174: 1261–1269.
70. Dubée V, Roy PM, Vielle B, *et al.* Hydroxychloroquine in mild-to-moderate coronavirus disease 2019: a placebo-controlled double blind trial. *Clin Microbiol Infect* 2021; 27: 1124–1130.
71. Schwartz I, Boesen ME, Cerchiaro G, *et al.* Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial. *CMAJ Open* 2021; 9: E693–E702.
72. Rajasingham R, Bangdiwala AS, Nicol MR, *et al.* Hydroxychloroquine as pre-exposure prophylaxis for coronavirus disease 2019 (COVID-19) in healthcare workers: a randomized trial. *Clin Infect Dis* 2021; 72: e835–e843.
73. Mitjà O, Corbacho-Monné M, Ubals M, *et al.* A cluster-randomized trial of hydroxychloroquine for prevention of covid-19. *N Engl J Med* 2021; 384: 417–427.
74. Skipper CP, Pastick KA, Engen NW, *et al.* Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med* 2020; 173: 623–631.
75. Si L, Bai H, Rodas M, *et al.* A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics. *Nat Biomed Eng* 2021; 5: 815–829.
76. Orrell C, Little F, Smith P, *et al.* Pharmacokinetics and tolerability of artesunate and amodiaquine alone and in combination in healthy volunteers. *Eur J Clin Pharmacol* 2008; 64: 683–690.
77. Borba MGS, Almeida Val FF, Sampaio VS, *et al.* Effect of high vs low doses of chloroquine

- diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open* 2020; 3: e208857.
78. Imai M, Iwatsuki-Horimoto K, Hatta M, *et al.* Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. *Proc Natl Acad Sci USA* 2020; 117: 16587–16595.
  79. Gonzalez Canga A, Sahagún Prieto AM, Diez Liébana MJ, *et al.* The pharmacokinetics and interactions of ivermectin in humans – a mini-review. *AAPS J* 2008; 10: 42–46.
  80. Boldescu V, Behnam MAM, Vasilakis N, *et al.* Broad-spectrum agents for flaviviral infections: dengue, Zika and beyond. *Nat Rev Drug Discov* 2017; 16: 565–586.
  81. Caly L, Druce JD, Catton MG, *et al.* The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020; 178: 104787.
  82. Sajid MS, Iqbal Z, Muhammad G, *et al.* Immunomodulatory effect of various anti-parasitics: a review. *Parasitology* 2006; 132(Pt3): 301–313.
  83. Yan S, Ci X, Chen N, *et al.* Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. *Inflamm Res* 2011; 60: 589–596.
  84. de Melo GD, Lazarini F, Larrous F, *et al.* Attenuation of clinical and immunological outcomes during SARS-CoV-2 infection by ivermectin. *EMBO Mol Med* 2021; 13: e14122.
  85. López-Medina E, López P, Hurtado IC, *et al.* Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. *JAMA* 2021; 325: 1426–1435.
  86. Buonfrate D, Chesini F, Martini D, *et al.* High-dose ivermectin for early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial. *Int J Antimicrob Agents* 2022; 59: 106516.
  87. Vallejos J, Zoni R, Bangher M, *et al.* Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. *BMC Infectious Diseases* 2021; 21: 635.
  88. Lim SCL, Hor CP, Tay KH, *et al.* Efficacy of ivermectin treatment on disease progression among adults with mild to moderate COVID-19 and comorbidities: the I-TECH randomized clinical trial. *JAMA Int Med* 2022; 182: 426–435.
  89. Temple C, Hoang R and Hendrickson RG. Toxic effects from ivermectin use associated with prevention and treatment of covid-19. *New Engl J Med* 2021; 385: 2197–2198.
  90. Reis G, Silva EASM, Silva DCM, *et al.* Effect of early treatment with ivermectin among patients with covid-19. *New Engl J Med* 2022; 386: 1721–1731.
  91. Ramos-Casals M, Brito-Zerón P and Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. *Nat Rev Rheumatol* 2021; 17: 315–332.
  92. Noreen S, Maqbool I and Madni A. Dexamethasone: therapeutic potential, risks, and future projection during COVID-19 pandemic. *Eur J Pharmacol* 2021; 894: 173854.
  93. Dexamethasone in hospitalized patients with covid-19. *New Engl J Med* 2020; 384: 693–704.
  94. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 2021; 384: 693–704.
  95. Tomazini BM, Maia IS, Cavalcanti AB, *et al.* Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020; 324: 1307–1316.
  96. Selvaraj V, Dapaah-Afryie K, Finn A, *et al.* Short-term dexamethasone in Sars-CoV-2 patients. *R I Med J* 2020; 103: 39–43.
  97. Lévesque V, Millaire É, Corsilli D, *et al.* Severe immune thrombocytopenic purpura in critical COVID-19. *Int J Hematol* 2020; 112: 746–750.
  98. Sheppard M, Laskou F, Stapleton PP, *et al.* Tocilizumab (Actemra). *Hum Vaccin Immunother* 2017; 13: 1972–1988.
  99. Sebba A. Tocilizumab: the first interleukin-6-receptor inhibitor. *Am J Heal-Syst Pharm* 2008; 65: 1413–1418.
  100. Zhao L, Yang Y, Li W, *et al.* Nivolumab-induced cytokine-release syndrome in relapsed/refractory Hodgkin's lymphoma: a case report and literature review. *Immunotherapy* 2018; 10: 913–917.
  101. Oved JH, Barrett DM and Teachey DT. Cellular therapy: immune-related complications. *Immunol Rev* 2019; 290: 114–126.
  102. McGonagle D, Sharif K, O'Regan A, *et al.* The role of cytokines including interleukin-6

- in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020; 19: 102537.
103. Mahroum N, Watad A, Bridgewood C, *et al.* Systematic review and meta-analysis of tocilizumab therapy versus standard of care in over 15,000 covid-19 pneumonia patients during the first eight months of the pandemic. *Int J Environ Res Public Health* 2021; 18: 9149.
  104. Xu X, Han M, Li T, *et al.* Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 2020; 117: 10970–10975.
  105. Jean SS and Hsueh PR. Old and re-purposed drugs for the treatment of COVID-19. *Expert Rev Anti Infect Ther* 2020; 18: 843–847.
  106. Salama C, Han J, Yau L, *et al.* Tocilizumab in patients hospitalized with covid-19 pneumonia. *New Engl J Med* 2020; 384: 20–30.
  107. Rosas IO, Bräu N, Waters M, *et al.* Tocilizumab in hospitalized patients with severe covid-19 pneumonia. *New Engl J Med* 2021; 384: 1503–1516.
  108. Wang D, Fu B, Peng Z, *et al.* Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. *Front Med* 2021; 15: 486–494.
  109. Interleukin-6 receptor antagonists in critically ill patients with covid-19. *New Engl J Med* 2021; 384: 1491–1502.
  110. Hermine O, Xavier Mariette X, Tharaux P-L, *et al.* Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Internal Medicine* 2021; 181: 32–40.
  111. Salvarani C, Dolci G, Massari M, *et al.* Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Int Med* 2021; 181: 24–31.
  112. Stone JH, Frigault MJ, Serling-Boyd NJ, *et al.* Efficacy of tocilizumab in patients hospitalized with Covid-19. *New Engl J Med* 2020; 383: 2333–2344.
  113. Veiga VC, Prats JAGG, Farias DLC, *et al.* Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ* 2021; 372: n84.
  114. Soin AS, Kumar K, Choudhary NS, *et al.* Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. *Lancet Respir Med* 2021; 9: 511–521.
  115. Zhang J, Chen C, Yang Y, *et al.* Effectiveness of tocilizumab in the treatment of hospitalized adults COVID-19: a systematic review and meta-analysis. *Medicine* 2022; 101: e28967–e28967.
  116. Al-Salama ZT and Scott LJ. Baricitinib: a review in rheumatoid arthritis. *Drugs* 2018; 78: 761–772.
  117. McInnes IB, Byers NL, Higgs RE, *et al.* Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations. *Arth Res Ther* 2019; 21: 183.
  118. Ivashkiv LB. Jak-STAT signaling pathways in cells of the immune system. *Rev Immunogenet* 2000; 2: 220–230.
  119. Shi JG, Chen X, Lee F, *et al.* The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. *J Clin Pharmacol* 2014; 54: 1354–1361.
  120. Hoang TN, Pino M, Boddapati AK, *et al.* Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell* 2021; 184: 460–475.e21.
  121. Marconi VC, Ramanan AV, de Bono S, *et al.* Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021; 9: 1407–1418.
  122. Estupiñán HY, Berglōf A, Zain R, *et al.* Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. *Front Cell Dev Biol* 2021; 9: 630942.
  123. von Hundelshausen P and Siess W. Bleeding by Bruton tyrosine kinase-inhibitors: dependency on drug type and disease. *Cancers* 2021; 13: 1103.
  124. Liu X, Zhang J, Han W, *et al.* Inhibition of BTK protects lungs from trauma-hemorrhagic shock-induced injury in rats. *Mol Med Rep* 2017; 16: 192–200.
  125. Florence JM, Krupa A, Booshehri LM, *et al.* Inhibiting Bruton's tyrosine kinase rescues mice from lethal influenza-induced acute lung injury. *Am J Physiol-Lung Cell Mol Physiol* 2018; 315: L52–L58.

126. Sun L, Liu S and Chen ZJ. SnapShot: pathways of antiviral innate immunity. *Cell* 2010; 140: 436–436.e2.
127. Chang BY, Huang MM, Francesco M, *et al.* The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. *Arthritis Res Ther* 2011; 13: R115.
128. Roschewski M, Lionakis MS, Sharman JP, *et al.* Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol* 2020; 5: eabd0110.
129. Strich JR, Ramos-Benitez MJ, Randazzo D, *et al.* Fostamatinib inhibits neutrophils extracellular traps induced by COVID-19 patient plasma: a potential therapeutic. *J Infect Dis* 2021; 223: 981–984.
130. Tabassum N, Zhang H and Stebbing J. Repurposing fostamatinib to combat SARS-CoV-2-induced acute lung injury. *Cell Rep Med* 2020; 1: 100145.
131. Mocsai A, Ruland J and Tybulewicz VL. The SYK tyrosine kinase: a crucial player in diverse biological functions. *Nat Rev Immunol* 2010; 10: 387–402.
132. Hoepel W, Chen H-J, Geyer CE, *et al.* High titers and low fucosylation of early human anti-SARS-CoV-2 IgG promote inflammation by alveolar macrophages. *Sci Transl Med* 2021; 13: eabf8654.
133. Kost-Alimova M, Sidhom E-H, Satyam A, *et al.* A high-content screen for mucin-1-reducing compounds identifies fostamatinib as a candidate for rapid repurposing for acute lung injury. *Cell Rep Med* 2020; 1: 100137.
134. Dhar P and McAuley J. The role of the cell surface mucin MUC1 as a barrier to infection and regulator of inflammation. *Front Cell Infect Microbiol* 2019; 9: 117.
135. Lu W, Liu X, Wang T, *et al.* Elevated MUC1 and MUC5AC mucin protein levels in airway mucus of critical ill COVID-19 patients. *J Med Virol* 2021; 93: 582–584.
136. Strich JR, Tian X, Samour M, *et al.* Fostamatinib for the treatment of hospitalized adults with COVID-19: a randomized trial. *Clin Infect Dis* 2022; 75: e491–e498.
137. Mallat Z, Lobo SM, Malik A, *et al.* 561. Phase 3 trial of fostamatinib for the treatment of COVID-19: repurposing an immunomodulatory drug previously approved for immune thrombocytopenia. *Open Forum Inf Dis* 2021; 8(Suppl. 1): S382–S383.
138. Moreno S, Perno CF, Mallon PW, *et al.* Two-drug vs. three-drug combinations for HIV-1: do we have enough data to make the switch? *HIV Med* 2019; 20(Suppl. 4): 2–12.
139. Gandhi S, Klein J, Robertson AJ, *et al.* De novo emergence of a remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report. *MedRxiv* 2022; 13: 1547.
140. Akinbolade S, Coughlan D, Fairbairn R, *et al.* Combination therapies for COVID-19: an overview of the clinical trials landscape. *Br J Clin Pharmacol* 2022; 88: 1590–1597.
141. Bosaeed M, Mahmoud E, Alharbi A, *et al.* Favipiravir and hydroxychloroquine combination therapy in patients with moderate to severe COVID-19 (FACCT Trial): an open-label, multicenter, randomized, controlled trial. *Infect Dis Ther* 2021; 10: 2291–2307.
142. Cavalcanti AB, Zampieri FG, Rosa RG, *et al.* Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *New Engl J Med* 2020; 383: 2041–2052.
143. Hung IF-N, Lung K-C, Tso EY-K, *et al.* Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020; 395: 1695–1704.
144. Li H, Xiong N, Li C, *et al.* Efficacy of ribavirin and interferon-alpha therapy for hospitalized patients with COVID-19: a multicenter, retrospective cohort study. *Int J Infect Dis* 2021; 104: 641–648.
145. Sleijfer S, Bannink M, Van Gool AR, *et al.* Side effects of interferon-alpha therapy. *Pharm World Sci* 2005; 27: 423–431.
146. Boriskin YS, Pécheur EI and Polyak SJ. Arbidol: a broad-spectrum antiviral that inhibits acute and chronic HCV infection. *Virol J* 2006; 3: 56.
147. Alavi Darazam I, Shokouhi S, Mardani M, *et al.* Umifenovir in hospitalized moderate to severe COVID-19 patients: a randomized clinical trial. *Int Immunopharmacol* 2021; 99: 107969.
148. Abbaspour Kasgari H, Moradi S, Shabani AM, *et al.* Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. *J Anti Chemother* 2020; 75: 3373–3378.
149. Abbass S, Kamal E, Salama M, *et al.* Efficacy and safety of sofosbuvir plus daclatasvir or

- ravidasvir in patients with COVID-19: a randomized controlled trial. *J Med Virol* 2021; 93: 6750–6759.
150. El-Bendary M, Abd-Elsalam S, Elbaz T, *et al.* Efficacy of combined Sofosbuvir and Daclatasvir in the treatment of COVID-19 patients with pneumonia: a multicenter Egyptian study. *Expert Rev Anti Infect Ther* 2022; 20: 291–295.
151. Schultz DC, Johnson RM, Ayyanathan K, *et al.* Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2. *Nature* 2022; 604: 134–140.
152. Peters GJ. Re-evaluation of Brequinar sodium, a dihydroorotate dehydrogenase inhibitor. *Nucleosides Nucleotides Nucleic Acids* 2018; 37: 666–678.
153. Shytaj IL, Fares M, Gallucci L, *et al.* The FDA-approved drug cobicistat synergizes with remdesivir to inhibit SARS-CoV-2 replication in vitro and decreases viral titers and disease progression in Syrian hamsters. *mBio* 2022; 13: e0370521.
154. Chen J, Xia L, Liu L, *et al.* Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. *Open Forum Infect Dis* 2020; 7: ofaa241.
155. Zanger UM and Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013; 138: 103–141.
156. A neutralizing monoclonal antibody for hospitalized patients with covid-19. *New Engl J Med* 2020; 384: 905–914.
157. Kalil AC, Patterson TF, Mehta AK, *et al.* Baricitinib plus remdesivir for hospitalized adults with covid-19. *New Engl J Med* 2020; 384: 795–807.
158. Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, *et al.* Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study. *Rheumatology* 2020; 60: 399–407.

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