Review

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Antimicrobials in COVID-19: strategies for treating a COVID-19 pandemic

https://doi.org/10.1515/jbcpp-2022-0061
Received February 26, 2022; accepted March 28, 2022;
published online May 3, 2022

Abstract: The COVID-19 pandemic continues to pose a serious global challenge, with the world engulfed in fighting second, third and fourth waves of the disease, which is reaching scary proportions in terms of cases and mortality in countries like India. Despite the urgent need of proven management protocols, there is still confusion about the best practices for treating COVID-19 with different pharmaceutical interventions. Antimicrobials are empirically used in COVID-19 patients. During the initial phase of this pandemic, hydroxychloroquine, ivermectin, azithromycin and doxycycline were widely suggested for possible prophylaxis or treatment for COVID-19 in outpatient as well as hospitalized settings. Various national and international guidelines recommended its use. However, cumulative evidence from subsequent clinical trials has revealed no significant clinical benefits in any setting, with the risk of adverse effects being high particularly in combination with azithromycin. Yet, there is continued use of antimicrobials particularly in outpatient settings which should be avoided because there is no justifiable rationale for doing so. Antimicrobial resistance (AMR) was one of the top problems for global public health before the coronavirus 2019 (COVID-19) pandemic began. AMR, which is already a difficult problem, must now be handled in the context of a changing healthcare sector.

Keywords: antimicrobial resistance; challenges; COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) pandemic caused by the novel coronavirus SARS-CoV-2 has posed a serious threat to public health on a global scale. After experiencing first and second wave, cases are rising once again and are approaching monstrous proportions—the current tally in India, stands at more than 3.4 crore cases, including about 4.72 lakh active cases and 4.83 lakh deaths, according to official figures [1]. These are alarming figures for a country with pre-existing healthcare deficiencies that are now being revealed by the exponential increase in the number of individuals requiring hospitalization and medical care. Even more difficult is the lack of proven treatment options and emergence of new variants that have exacerbated this issue further. Despite the best efforts of the medical and research communities all around the world to discover effective treatment modality, some treatments have obtained conditional approval, but none of them has yet proven to be truly transformative [2]. While the treatment approaches are clear, the management recommendations or guidelines are still not definitive in terms of including or excluding the various treatment options being tried for mild, moderate, or severe COVID-19, such as ivermectin, azithromycin, doxycycline, hydroxychloroquine, favipiravir, remdesivir and molnupiravir. Many of the medications that are regularly recommended in India for both hospitalised and non-hospitalized patients now lack conclusive or even strongly suggestive global or Indian evidence [3, 4] (Table 1 and Figure 1).

Hydroxychloroquine (HCQ)

A 4-aminoquinoline, with antimalarial, anti-autophagy and immunomodulatory activity, suppresses immune system by interfering with antigen processing and presentation, and with cytokine development. It shows its lysosomotropic property by causing accumulation of ineffective autophagosomes, which results in cell death in tumour cells. It is highly effective anti-malarial agent by acting against plasmodium species [5].

Evidence from *In vitro*/*In vivo* studies

In vitro studies, HCQ works against SARS CoV-2 by inhibiting glycosylation of host ACE-2 receptors, proteolytic processing,

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Table 1: Summary of study characteristics and outcomes.

Sr No.	Study	Groups	Type of study No. of patients	Conclusion
HCQ/CQ				
1.	Ghazy RM et al. [9]	(a) HCQ or CQ in comparison to standard of care (SC) (b) HCQ + AZM in comparison to SC	Systematic review and meta-analysis (14 randomized control trials) Sample size ranged from 30 to 1,438 participants	When CQ/HCQ was used alone or in combination with AZM, duration of hospital stay was increased. Treating with CQ/HCQ did not decrease mortality besides it was increased if AZM was added
2.	Tang W et al. [10]	HCQ plus standard of care compared with standard of care alone	Open label RCT 150 adults hospitalised	Administration of HCQ did not result in a significantly higher probability of negative conversion than standard of care alone in patients admitted to hospital with mainly persistent mild to moderate COVID-19
3.	Skipper CP et al. [11]	Oral HCQ or masked placebo	Randomized, double-blind, placebo-controlled trial double-blind RCT 400 symptomatic non-hospitalized	HCQ did not substantially reduce symptom severity in outpatients with early, mild COVID-19
4.	Cheng MP et al. [12]	Two groups, either with HCQ or without HCQ	Randomized controlled trials 63 COVID-19 patients	Little or no significant improvement
5.	Singh B et al. [13]	Nine trials compared HCQ with standard care (7,779 participants), and one compared HCQ with placebo (491 participants)	Randomized controlled trials Involving 8,000 patients	HCQ has little or no effect on the risk of death and probably no effect on progression to mechanical ventilation. Adverse events are tripled compared to placebo
6.	WHO Solidarity trial Consortium [14]	Five options, four active and the local standard of care remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a	Multicentred Randomized controlled trials 14,200 patients	Little or no impact of HCQ on hospitalised COVID-19 patients as indicated by overall mortality, initiation of ventilation, and duration of hospital stay
7.	RECOVERY Collaborative group [15]	1,561 patients received hydroxychloroquine and 3,155 received usual care	Multicentred Randomized controlled trials 4,716 patients	Patients in the HCQ group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6 vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98)
8.	Mitjà O et al. [16]	HCQ vs usual-care group (which received no specific therapy)	Open-label, cluster-randomized trial 2,314 healthy contacts of 672 index case patients	Post-exposure therapy with HCQ did not prevent. SARS-CoV-2 infection or symptomatic COVID-19 in healthy persons exposed to a PCR-positive case patient
Ivermectin				
9.	Pierre K et al. [37]		Meta-analyses based on 18 randomized controlled treatment trials	Large statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance
10.	Kim MS et al. [38]		Systematic review and network meta-analysis 110 studies (40 RCTs and 70 observational studies)	HCQ did not provide clinical benefits while posing cardiac safety risks when combined with azithromycin, especially in the vulnerable population
11.	Garegnani LI et al. [39]	Ivermectin vs standard of care or placebo	Meta-analysis	Research related to ivermectin in COVID-19 has serious methodological limitations resulting in very low certainty of the evidence, and continues to grow

Table 1: (continued)

Sr No.	Study	Groups	Type of study No. of patients	Conclusion
12.	Elgazzar A et al. [42]	Ivermectin plus standard care (azithromycin, vitamin C, zinc, lactoferrin and acetylcystein and prophylactic or therapeutic anticoagulation hydroxychloroquine plus standard of care	Multicentre randomized controlled clinical trial 600 subjects; 400 symptomatic confirmed COVID-19 patients and 200 health care and household contacts	Ivermectin to standard care is very effective drug for treatment of COVID-19 patients with significant reduction in mortality compared to HCQ plus standard treatment only. Early use of ivermectin is very useful for controlling COVID 19 infections, prophylaxis and improving cytokines storm
Azithromycin				
13.	PRINCIPLE trial Collaborative group [53]	Azithromycin (n= 500) vs. usual NHS care only (n= 823)	Randomized controlled clinical trial 1,323 patients	Azithromycin is not an effective treatment for reducing the time to recovery or risk of hospital admission for people with suspected COVID-19 in the community
14.	RECOVERY Collaborative group [54]	Standard of care alone or usual standard of care plus azithromycin 500 mg once per day by mouth or intravenously for 10 days or until discharge	Randomized controlled clinical trial	Azithromycin did not improve survival or other prespecified clinical outcomes and should be restricted to patients in whom there is a clear antimicrobial indication
15.	Cavalcanti AB et al. [55]	Standard care vs. standard care plus HCQ at a dose of 400 mg twice daily, or standard care plus HCQ at a dose of 400 mg twice daily plus azithromycin at a dose of 500 mg once daily for seven days	Multicentre, randomized, open-label, three-group, controlled trial 667 patients	A 7-day course of HCQ either with azithromycin or alone did not result in better clinical outcomes as measured by a seven-level ordinal scale at 15 days
16.	Furtado RHM et al. [56]	Azithromycin (500 mg) plus standard of care or to standard of care without macrolides patients received HCQ (400 mg twice daily for 10 days)	Open-label, randomised clinical trial at 57 centres in Brazil 447 patients	Adding azithromycin to standard of care treatment did not improve clinical outcomes
Remdesivir				
17.	Lai CC et al. [70]	Compared with placebo, standard of care, or different treatment regimens of remdesivir	Systematic review and network meta-analysis of randomized controlled trials (RCTs) 13,544 patients	Remdesivir helps improve the clinical outcome of hospitalized patients with COVID-19 and a five day regimen, instead of a 10 day regimen, may be sufficient for treatment
18.	Piscoya A et al. [71]	2 RCTs vs. placebo and two comparing 5-day vs. 10-day regimens	A systematic review and meta-analysis 4 RCT and 2 case series 4,680 pts	There is paucity of adequately powered and fully reported RCTs evaluating effects of remdesivir in hospitalized COVID-19 patients
19.	Rezagholizadeh A et al. [72]	Compared with placebo	Systematic review and meta-analysis 10 studies, including 5 RCTs and 5 NRSIs 8,583 patients	Significant improvement in the 28-day recovery rate, low flow oxygen support through the baseline to day 14
20.	Wilt TJ et al. [73]	Compared with placebo	A living systematic Review 4 randomized trials	Remdesivir improves recovery and reduces serious adverse events and may reduce mortality and time to clinical improvement
21.	Bansal V et al. [74]	Compared with placebo	A systematic Review and meta-analysis 1,895 patients from 9 studies	Mortality benefit with Remdesivir in COVID-19 and median recovery time was over 2 weeks

Table 1: (continued)

Sr No.	Study	Groups	Type of study No. of patients	Conclusion
Molnupiravir				
22.	Lee CC et al. [83]	Compared with placebo	Review of double-blind, randomized-controlled, multicentre 2 phase I studies 2 phase II studies 2 phase phase-II/III trials 2,434 patients	Molnupiravir significantly reduced the risk of hospitalization or death in adults experiencing mild or moderate COVID-19
23.	Khoo SH et al. [85]	Compared with control	Phase Ib/IIa open-label, dose-escalating, randomized controlled study 20 patients	Molnupiravir was safe and well tolerated, a dose of 800 mg twice daily for five days was recommended for phase II evaluation
24.	Fischer WA et al. [87]	Compared with placebo	Phase IIa 404 patients	Molnupiravir is the first oral, direct-acting antiviral shown to be highly effective at reducing nasopharyngeal SARS-CoV-2 infectious virus and viral RNA and has a favorable safety and tolerability profile
25.	Jayk Bernal A et al. [88]	Compared with control	Phase 3, double-blind, randomized, placebo-controlled trial 1,433 participants	Early treatment with molnupiravir reduced the risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19
Favipiravir				
26.	Dabbous HM et al. [100]	CQ group vs. favipiravir group	Multi-centre randomized study 96 patients	Favipiravir is a promising drug for COVID-19 that decreases the hospital stay and the need for mechanical ventilation
27.	Cai Q et al. [101]	Favipiravir (FPV) vs. lopinavir (LPV)/ritonavir (RTV)	An open-label control study 80 patients	FPV showed better therapeutic responses on COVID-19 in terms of disease progression and viral clearance
28.	Manabe T et al. [103]	Comparators included were umifenovir, baloxavir marboxil, standard of care, lopinavir/ritonavir, and HQ alone or in combination with azithromycin	Systematic review and meta-analysis 11 studies (3 RCT, 1 NRCT, 1 study was a before and after non-randomized controlled study, and 6 studies were observational studies or case series	Favipiravir group exhibited significantly better viral clearance on day 7 after the initiation of treatment and clinical improvement was significantly better in the favipiravir group on both days 7 and 14 days
29.	Hassanipour S et al. [104]	Favipiravir vs. the control	Systematic review and meta-analysis Nine studies were included in our meta-analysis 827 patients	Significant clinical improvement in the favipiravir group vs. the control group during seven days after hospitalization
30.	Udwadia ZF et al. [105]	Oral favipiravir (day 1: 1800 mg BID and days 2–14: 800 mg BID) plus standard supportive care vs. supportive care alone	Randomized, comparative, open-label, multicentre, phase III clinical trial 147 patients	Significant improvement in time to clinical cure suggests favipiravir may be beneficial in mild-to-moderate COVID-19
Doxycycline				
31.	Butler CC (PRINCIPLE trial) [116]	Usual care only, usual care plus oral doxycycline (200 mg on day 1, then 100 mg once daily for the following six days), or usual care plus other interventions	Open-label, multi-arm, adaptive platform randomised trial	Treatment with doxycycline was not associated with clinically meaningful reductions in time to recovery or hospital admissions or deaths related to COVID-19, and should not be used as a routine treatment for COVID-19

Table 1: (continued)

Sr No.	Study	Groups	Type of study No. of patients	Conclusion
32.	DYNAMIC study (Doxy-cYcliNe AMbulatoIre COVID-19) (DYNAMIC) [118]	Doxycycline vs. a placebo	Multicentre, Randomized, double-blind study, phase III 330 participants	Showed promising results

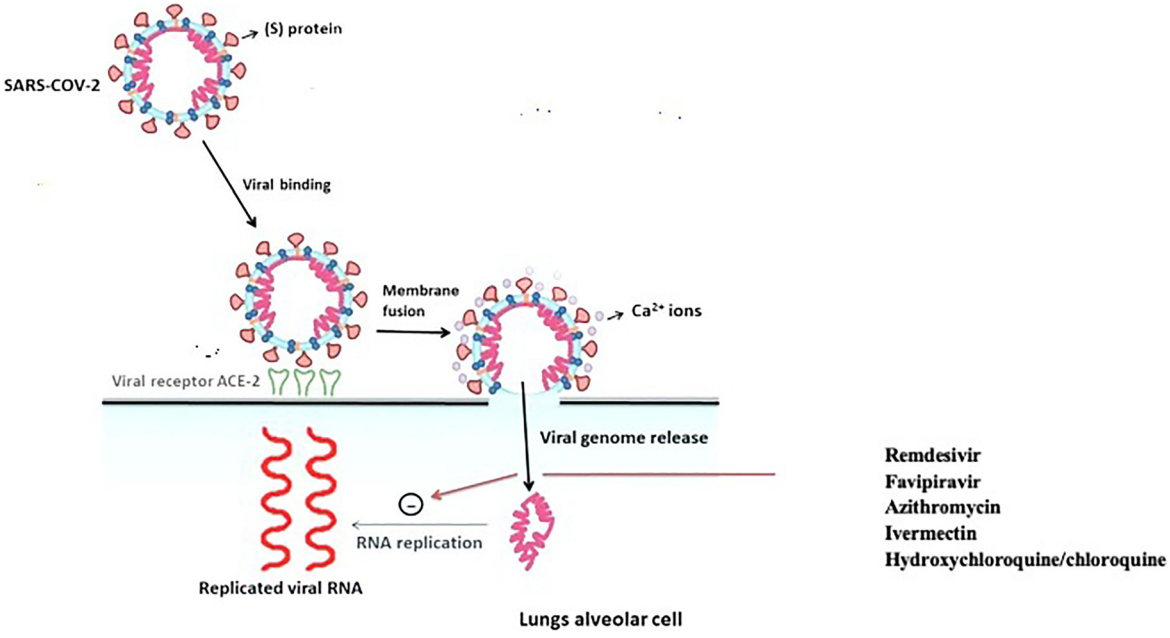

Figure 1: Diagram showing drugs blocking replication of SARS-CoV-2.

and endosomal acidification in viral cells. Drug also shows its immunomodulatory activities and preventing nucleic acid replication [6, 7]. When chloroquine/HCQ was administered after infection began, the number of virus antigen-positive cells decreased dramatically in a dose-dependent manner. Chloroquine/HCQ doses of 0.1–1 M inhibited infection by 50%, whereas concentrations of 33–100 M inhibited infection by 90–94%. Only a limited number of individual cells were initially infected at chloroquine concentrations more than 1 M, and the transmission of infection to neighbouring cells was virtually eliminated. These findings clearly suggest that adding chloroquine soon after virus adsorption can significantly limit the establishment of infection and transmission of SARS-CoV [7, 8].

Evidence from clinical studies

Many studies have looked at hydroxychloroquine alone or in combination with azithromycin (AZM) in COVID-19 patients, especially in hospitalised patients, although there have been fewer in non-hospitalized settings or in mild to moderate COVID-19 patients. Meta analyses and systematic reviews (including both interventional and observational studies) found no or inconclusive proof of a benefit of HCQ, and a number of trials were stopped early due to enrolment issues and emerging evidence that HCQ is not an effective treatment option [9, 12]. According to the Cochrane review on the use of chloroquine or HCQ, which included only randomized controlled trials (RCTs) (n=12) the analyses on

more than 8,000 patients found no significant reduction in risk of mortality (RR 1.09, 95% CI 0.99–1.19), no differences in virological cure or disease progression, and a significant increase in risk of adverse events (RR 2.90, 95%), with varied degrees of bias, the heterogeneity was determined to be considerable [13]. Results from the two largest global RCTs – WHO Solidarity trial and UK RECOVERY- have also shown that hydroxychloroquine appears to have little or no impact on hospitalized COVID-19 patients, as shown by total mortality, ventilation initiation, and hospital stay length [14, 15]. In multicentred, open label RCT in Spain, HCQ was given in a regimen of 800 mg on day 1, followed by 400 mg once day for 6 days, to 293 non-hospitalized adult patients with mild COVID-19, and was compared to conventional therapy (no antiviral treatment). There were no significant differences in virological load reduction, cure, or risk of hospitalization (RR 0.75, 95% CI 0.32–1.77) or time to complete resolution of symptoms (10 vs. 12 days, p=0.38) [16]. Similar results were shown by double-blind RCT conducted across the United States and Canada [11].

Current recommendations

During the early stages of the pandemic, hydroxychloroquine was extensively mentioned as a viable COVID-19 prophylactic or treatment. HCQ was also recommended in India for the treatment of mild COVID-19 initially, with the most recent version of the national COVID-19 clinical management guidelines, released in April 2021 jointly by the Indian Council of Medical Research (ICMR) and the All India Institute of Medical Sciences (AIIMS) New Delhi, recommending a dosing regimen of 400 mg BD for one day, followed by 400 mg OD for four days [17, 18]. The World Health Organization (WHO) now strongly advises against using hydroxychloroquine or chloroquine in the treatment of any severity of COVID-19 [19], while the Infectious Diseases Society of America (IDSA) panel and the US National Institutes of Health (NIH) guidelines advised against using it in hospitalised patients [20, 21]. The US FDA likewise revoked HCQ's emergency use authorisation (EUA) since the hazards discovered outweighed the potential benefits of use [22, 23]. When taken in high doses or for long periods of time, HCQ has been known to produce cardiac adverse effects such as bundle-branch or AV block, QT prolongation and subsequent "torsade de pointes," increased risk of arrhythmias, cardiac collapse and cardiomyopathy [24].

Ivermectin

The data from *in-silico*, *in vivo*, *in vitro* research, observational studies, clinical trials and meta-analysis, has been available to date have been a source of contention. Although the potential negative environmental effects of ivermectin in animal medicine are well known, the potential ecotoxicological effects of human use have gotten less attention [25].

Evidence of *in silico* activity of ivermectin against SARS-CoV 2

In-silico investigations show that ivermectin binds to a variety of target proteins with varying affinities, including the spike protein S2 subunit, SARS-CoV-2-DNA-dependent polymerase (RDRP), and TMPRSS2. Ivermectin have a role in inhibiting *N*-phosphoprotein and M proteins, as well in interfering with nuclear import. The nucleocapsid protein's moderately successful binding could indicate that nucleocapsid activity is harmed following trans-nuclear import. SARS-CoV-2 nuclear translocation was similarly inhibited by ivermectin. Binding with spike protein and TMPRSS2 has been shown to have a key function in blocking virus entrance into the host cell. The multi-target nature of ivermectin against SARS-CoV2 is demonstrated by these data [26–28].

Evidence from *in vitro* studies for use of ivermectin against SARS-CoV2

In a systematic review, Heidary et al. found that ivermectin had antiviral activity against a wide range of RNA and DNA viruses. They concluded that ivermectin could be useful in preventing or treating COVID-19 in its early phases [29]. In a study demonstrating the *in vitro* antiviral action of ivermectin, infected Vero/hSLAM cells were incubated with 5 M ivermectin for 48 h, resulting in a 5000-fold reduction of viral RNA in ivermectin treated samples compared to control samples. Ivermectin's IC50 was discovered to be around 2.5 M. These concentrations are 50–100 times the peak concentration (C_{max}) observed in plasma after a single dosage of 200 g/kg (12 mg adult dose) routinely utilized in clinical trials [30, 31]. In mouse models, the considerable effectiveness of ivermectin in cell culture has not been replicated. This is most likely due to ivermectin's pharmacokinetics and safety characteristics. The highest detected plasma concentration in mice was 186.7 ng/mL, which corresponds to 0.21 M/L, which is substantially lower than Caly

et al. reported half-maximal inhibitory concentration (IC50) 2 M [32]. In Dengue virus infected Vero cells, Wagstaff et al. found inhibition at significantly greater *in vitro* concentrations (25 M) [33].

Evidence regarding dosing from *in vivo* studies

A once-daily dose of ivermectin 400 g/kg for three days was shown to be safe but did not produce any therapeutic benefit in one of Thailand's phase III clinical trials on dengue patients [34]. Jermain et al. created a physiologically based pharmacokinetic model to simulate ivermectin exposure to human lungs when given in oral dosages (12, 30, and 120 mg). The simulated ivermectin exposure to the lungs resulted in a concentration of 772 ng/mL, which was significantly lower than the reported *in vitro* IC50 for ivermectin (1750 ng/mL) [35]. As a result, standard dosages are unlikely to be sufficient to elicit antiviral activity against SARS-CoV2.

Evidence from clinical trials on use of ivermectin in COVID-19

The results of studies using ivermectin for chemoprophylaxis in COVID-19 have been mixed and contradictory. Ivermectin had no statistically significant differences in reducing the frequency of SARS-CoV-2 infection, and neither statistically significant absolute risk reductions were observed in a randomized controlled experiment done in Singapore [36].

A widely varying dose range was observed among 18 trials assessed in the study, which reported excellent results for the treatment of ivermectin in COVID-19 in terms of reductions in time to clinical recovery, time to viral clearance, and death. There were no dose regimens that were similar in any of the other studies. The doses ranged from 0.2 mg/kg given once to 12 mg given every seven days [37]. Another systematic review and meta-analysis of ivermectin safety and efficacy in hospitalized COVID-19 patients comprised 110 papers. There were 78 randomized clinical trials and 32 observational studies among the 110 studies. Ivermectin was found to be associated with a lower mortality rate in critically ill patients in this investigation. However, like in the prior analysis, overall evidentiary certainty was determined to be quite low [38]. In reporting the efficacy of ivermectin in COVID-19, there were some severe methodological flaws in the clinical investigation. As many of these researches have been published in protocol repositories and pre-prints, they do not meet publication quality criteria. The peer-reviewed papers evaluating the efficacy of ivermectin in COVID-19 revealed significant variation in doses, patient populations and research types, implying a poor level of confidence in the evidence for applying findings in clinical practise [39].

Current recommendations

Ivermectin has not been authorized by the US Food and Drug Administration for use in humans to treat or prevent COVID-19 [40]. In response to the increased international attention on ivermectin as a potential treatment for COVID-19, an independent guideline development group (which includes an international panel of experts, clinical care experts in multiple specialties, as well as an ethicist and patient-partners) was convened. They analyzed data from 16 randomized controlled trials (with a total of 2,407 participants), which included both inpatients and outpatients with COVID-19. Due to the small sizes and methodological limitations of available trial data, including a small number of patients, they concluded that the evidence on whether ivermectin reduces mortality, need for mechanical ventilation, need for hospital admission, and time to clinical improvement in COVID-19 patients is of "very low certainty [41]". In the EU, ivermectin is not approved for use in COVID-19 [42]. Ivermectin was once given in India, but it was removed from the ICMR/AIIMS COVID-19 management recommendations for the treatment of moderate COVID-19 [43].

Azithromycin

Azithromycin is a macrolide antibiotic that has both bacteriostatic and bactericidal properties. It inhibits bacterial protein synthesis by reversibly binding to the sensitive microorganisms' 50S ribosomal subunit, preventing the translocation process and resulting in cell growth suppression and death [44]. The approved indications are community-acquired pneumonia (CAP), mild to moderate upper respiratory tract infections (RTI), uncomplicated enteric fever, uncomplicated skin and skin structure infections, pelvic inflammatory disease (non-gonococcal urethritis, cervicitis), acute otitis media in adults and children etc. [45, 46]. In addition to its antibacterial properties, this macrolide also shows antiviral and immunomodulatory properties that have been studied in viral infections, including COVID-19. It has been shown in preclinical investigations to have antiviral properties against the Zika, Rhino and Ebola viruses [45, 46].

Evidence from *In silico*/*In vitro*/*In vivo* studies

According to in-silico and other studies, azithromycin's putative mechanisms of action in the treatment of COVID-19 are mostly dependent on its immunomodulatory activity in addition to its antiviral effect. It prevents SARS-CoV-2 from attaching to host cells by raising the pH of the trans-Golgi network, which changes the glycosylation of the human ACE2 (hACE2) receptor and inhibits the spike protein's binding to target cells. It can also disrupt membrane fusion and endocytosis by interfering with ligand CD147 receptor contacts [47–49]. It reduces pro-inflammatory cytokines and chemokines such Interleukin (IL)-1, IL-6, IL-8, IL-12, Interferon (IFN)-, IP-10, tumour necrosis factor (TNF)- and GM-CSF, and suppresses CD4+ T-cell activation. Increased apoptosis, antifibrotic efficacy via suppression of fibroblast proliferation, reduction of collagen formation, decreased transforming growth factor (TGF) production and inhibition of TGF-induced pro-fibrotic gene stimulation have also been reported [50–52].

Evidence from clinical studies

The results of a few large, well-designed, adequately powered randomized clinical trials (RCTs) conducted to assess the effect of azithromycin monotherapy, specifically in the treatment of mild-moderate COVID-19, primarily in the UK and Brazil, have now been published, resulting in higher quality evidence. The PRINCIPLE trial [53], primary care (community based), open-label, multi-arm, randomized trial of treatments testing azithromycin use in 2,265 non-hospitalized COVID-19 patients was conducted in U.K. There was very little evidence of a meaningful benefit in the azithromycin group in terms of time to first reported recovery (hazard ratio 108; 95% confidence interval 095 to 123 vs. conventional therapy alone), requirement for hospitalization, and death at 28 days. Evidence from this study does not support the routine use of azithromycin for COVID-19 in community or hospital settings [53]. Prior to this, the RECOVERY trial [54] was conducted on hospitalized COVID-19 patients (n=7,763), in which 2,582 patients were randomly assigned to receive azithromycin (500 mg once daily orally or intravenously for 10 days or until discharge) and 5,181 patients were randomly assigned to receive usual care alone. Patients who did not or did require oxygen support at baseline, as well as those who required ventilatory assistance (i.e. mild/moderate/severe COVID-19), were included in this group. There was no difference in 28-day mortality (Rate ratio 097, 95% CI 087–107; p=050), length of stay (median 10 days [IQR 5 to >28] vs. 11 days [5 to >28]), or the composite endpoint of invasive mechanical ventilation or death (Rate ratio 097, 95% CI 087–107; p=050). At 15 days, the azithromycin group's outcomes were shown to be worse. Other research studies like COALITION-I and COALITION-II research, also reported statistically non-significant results, and concluded that azithromycin to normal therapy had no effect on clinical outcomes [55, 56].

Current recommendations

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued a COVID-19 therapeutic alert in January 2021, stating that azithromycin (as well as doxycycline) should not be used within primary care for the treatment of COVID-19 [57]. While scientific bodies have suggested that azithromycin's antibacterial properties may continue to be useful in the empirical treatment of CAP in COVID-19 patients, and that it has also been useful in influenza associate pneumonia, the evidence for its direct activity in COVID-19 has been largely inconclusive [58, 59]. Due to a lack of high-quality evidence in favour and concerns about possible side effects, all major international guidelines (WHO, NIH, IDSA) strongly advise against using azithromycin with hydroxychloroquine [60–62], and a similar nature of recommendation exists for azithromycin alone, though with less certainty. There is substantial evidence and reports that azithromycin use has increased over the world, particularly in India, during the COVID-19 pandemic [63–65].

Remdesivir

Remdesivir is a SARS Cov-2 experimental, directly acting antiviral medication that was first developed for hepatitis C (2009) but failed. It is a broad-spectrum antiviral drug that works by preventing virus replication inside host cells by inhibiting RNA dependent RNA polymerase (RdRp). There may also be binding to Mpro (main protease), which is responsible for replicative protein release; this could have a synergistic effect [66, 67].

Evidence from *in vitro* studies

Warren et al. showed, that remdesivir incorporates into nascent viral RNA chains and results in pre-mature termination. In non-human primate (NHP) model, intravenous administration of 10 mg/kg dose of remdesivir resulted in

concomitant persistent levels of its active form in the blood (10 μM) and conferred 100% protection against Ebola virus infection [68]. Another study showed that EC90 value of remdesivir against 2019-nCoV in Vero E6 cells was 1.76 μM, suggesting its working concentration is likely to be achieved in NHP. This study concluded that remdesivir also inhibited virus infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to 2019-nCoV [69].

Evidence from clinical studies

Five significant phase III RCTs evaluating remdesivir therapy in hospitalized mild to severe COVD-19 patients were included in a meta-analysis by Lai CC et al.; More than 13,000 patients were enrolled in these properly powered studies, with over 4,000 of them receiving remdesivir as a 10-day (all 5 RCTs) or 5-day (2 RCTs) regimen of 200 mg on day 1 followed by 100 mg (i.v. infusions) from days 2–5 or 10. Most clinical outcomes investigated revealed significant benefits of remdesivir therapy compared to control, with the exception of mortality, which showed a non-significant trend toward lower mortality. Both the 10 and 5-day regimens significantly improved outcomes (OR > 1 – both point estimates and 95% confidence intervals), but the 5-day regimens tended to show greater benefits for outcomes like clinical improvement (at least 2 points on a 7-point ordinal scale, OR 1.68, 95% confidence interval 1.18–2.401), likelihood of discharge and recovery, as well as shorter time to recovery and clinical improvement – all of which showed greater odds in the 5 day treatment regimen [70].

Aside from this study, a number of other meta-analyses have been published, with results that are largely consistent. The 28-day mortality risk was 44% lower in the remdesivir group, according to Rezagholizadeh A et al.'s meta-analysis of non-randomized interventional studies. It also demonstrated that remdesivir treatment had significant improvements on low flow oxygenation up to day 14 and invasive breathing demand from days 14–28 in RCTs [71–74].

Current recommendations

Remdesivir is the first medicine to get complete approval from the US Food and Drug Administration (FDA) in November 2020 for COVID-19, while EUA has been extended to children under the age of 12 [75]. Remdesivir has a conditional approval in the United Kingdom and Europe for hospitalized adolescents (12 years of age) and adults with pneumonia who require supplementary oxygen or non-invasive ventilation, in addition to the United States. As a result, both the UK NICE and the US NIH recommendations advise using remdesivir in these patients (but not for those requiring invasive mechanical ventilation) [76]. Similarly, the BMJ best practices guidelines advise against using remdesivir at this time, stating no significant differences in occurrences per thousand calculated for a variety of critical outcomes and describing the evidence as of low quality [77].

Molnupiravir

Molnupiravir is the N4-hydroxycytidine iso-propyl ester prodrug. It binds to RNA virus genomes, resulting in a cascade of mutations known as viral error catastrophe. This drug inhibits the replication of human and bat coronaviruses, including SARS-CoV-2, in mice and human airway epithelial cells. It was also discovered that a remdesivir-resistant mutant mouse hepatitis virus exhibits increased sensitivity to N4-hydroxycytidine [78].

Evidence from *in vitro* study

In vitro studies, molnupiravir resulted in potent antiviral efficacy with EC_{50} of 0.3 and 0.4 μM in Vero E6-GFP and Huh7 cells, respectively. Molnupiravir is known to increase the mutation frequency of MERS-CoV viral RNA in infected mice [79]. Another study determined the *in vitro* inhibitory effect of Molnupiravir on SARS-CoV-2 replication in Calu-3 cells (disease-relevant human lung epithelial cell line). Cells were pre-treated with differing drug concentrations and the effect on viral RNA load in tissue culture supernatant was determined at 24 h after infection by quantitative reverse transcriptase polymerase chain reaction. It resulted in a decrease in SARS-CoV-2 replication by approximately 3-logs (880-fold) when compared to no drug controls. The half-maximal inhibitory concentration (IC_{50}) value at sub-micromolar levels in Calu-3 cells at 414.6 nM. Viability was also assessed over the differing concentrations, demonstrating only minimal cellular toxicity at the highest drug concentration [80]. Wahl et al. [81] reported that EIDD 2801 significantly suppressed SARS-CoV-2 replication in human lung-only mice (LoM) *in vivo*. In a ferret model of influenza, the medication showed reduced viral shedding and inflammatory infiltrates in nasal lavages, as well as an adequate humoral antiviral response. Molnupiravir also had an inhibitory effect on SARS-CoV-2 multiplication in a Syrian hamster model when given 12 h before or after the experimental infection [81, 82]

Evidence from clinical studies

Oral molnupiravir is safe and well-tolerated at therapeutic doses, according to two phase-I trials (NCT04392219 and NCT04746183). In two phase-II trials, acceptable efficacy were revealed after five days of oral drug therapy, as measured by the elimination of nasopharyngeal virus in patients with early and mild COVID-19 [83–87]. These studies have shown that oral molnupiravir is highly efficient at reducing nasopharyngeal SARS-CoV-2 infection while also having a good tolerance and safety profile. Fischer et al. conducted research (Phase 2a) to assess the safety, tolerability, and antiviral activity of molnupiravir in the treatment of COVID-19 outpatients with confirmed SARS-CoV-2 infection and symptom onset within 7 days. Participants were randomised 1:1 to 200 mg of drug or placebo, twice daily for 5 days, or 3:1 to molnupiravir (400 or 800 mg) or placebo. The drug was well tolerated in all groups, with equal frequencies of side events. Molnupiravir was found to be highly effective at reducing nasopharyngeal SARS-CoV-2 infectious virus and viral RNA, as well as having a positive safety and tolerability profile, in this trial [88]. According to preliminary results of the trial (NCT04575597) released by Ridgeback Biotherapeutics, molnupiravir was shown to significantly reduced the risk of hospitalisation or mortality in non-hospitalized individuals with mild or moderate COVID-19 in 1850 non-hospitalized adults. This Drug treated patients had significantly lower rates of hospitalization or mortality within 29 days of randomization (28/385, 7.3% vs. 53/377, 14.1%; p=0.001) than placebo-treated patients (28/385, 7.3% vs. 53/377, 14.1%; p=0.001) [89]. In another phase 3 double-blind, randomized, placebo-controlled trials to evaluate the efficacy and safety of treatment with molnupiravir started within 5 days after the onset of signs or symptoms in 1,433 nonhospitalized, unvaccinated adults with mild-to-moderate, laboratory-confirmed COVID-19 Molnupiravir was found to be superior to placebo, the risk of hospitalisation for any reason or death was lower (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]) (difference, 6.8%-age points; 95% confidence interval, 11.3 to 2.4; p=0.001) [90].

Current recommendations

Drug was approved by the UK's Medicines and Health Products Regulatory Agency (MHRA) on November 4, 2021, to prevent severe COVID-19-related outcomes in adults, such as hospitalization and death. On December 23, 2021, the FDA gave emergency use authorization to molnupiravir; nevertheless, it is not yet fully approved [91]. Molnupiravir is not approved for usage in patients under the age of 18 and pregnant women because it can interfere with bone and cartilage formation and damages developing foetus. Indian Health authority has also expressed concerns regarding safety of this drug [92].

Favipiravir

Favipiravir (prodrug) is a purine base analogue that undergoes intracellular phosphor-ribosylation to become active favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP). It is a powerful and selective inhibitor of RNA virus RNA-dependent RNA polymerase (RdRp). It is integrated into the nascent viral RNA via the error-prone viral RdRp, resulting in viral mutagenesis and chain termination. Favipiravir-RTP has a beneficial effect on SARS-CoV-2 by inducing a cytopathic effect and mutation [93–96]. In 2014, favipiravir was approved in Japan to treat cases of influenza that were unresponsive to conventional treatment [97].

Evidence from *in vitro* studies

Favipiravir has proven efficacy against a broad range of influenza viruses, including A(H1N1)pdm09, A(H5N1) and A(H7N9) avian virus. Additionally, it may halt the replication of several other RNA viruses, including arenaviruses, phleboviruses, hantaviruses, flaviviruses, western equine encephalitis virus, noroviruses and ebola virus [98]. Favipiravir has a strong binding affinity to RdRp with a docking score of −6.925. Hence, favipiravir targets the RdRp complex of SARS-CoV-2 [99].

Evidence from clinical studies

In a study conducted by Dabbous et al., in 96 patients with confirmed SARS-CoV-2 infection to evaluate the efficacy of favipiravir for treatment of COVID-19. This was multicentred, interventional phase 2/phase 3 study in which patients were randomly assigned to receive chloroquine (CQ) (48 patients 600 mg tablets twice daily added to the standard-of-care therapy for 10 days) and favipiravir (1,600 mg twice a day on the first day and 600 mg twice a day from the second to tenth day), added to the standard-of-care therapy for 10 days. Although not statistically significant (p=0.06), the favipiravir group had a lower mean duration of hospital stay (13.29 ± 5.86 days) than the CQ group (15.89 ± 4.75 days) [100]. The effects of favipiravir vs. Lopinavir/ritonavir (LPV/RTV) for the treatment of COVID-19 were investigated in an open-label control research in Chinese (n=80) patients with mild to

moderate COVID-19. Favipiravir showed better results, with a faster viral clearance time (median [interquartile range, IQR] 4 [2.5–9] days vs. 11 [8–13] days). Favipiravir was found to be substantially (p=0.026) linked with faster viral clearance, and the timing of antiviral medication was found to be nearly significant (p=0.055). The drug was tolerated better (p=0.001) than LPV/RTV. The fact that this study was not randomized, double-blinded or placebo-controlled was a serious flaw [101, 102]. Toshie Manabe et al., performed systematic and meta-analysis to compare the control group (placebo, standard of care (SOC), remdesivir, lopinavir/ritonavir, other available antivirals, hydroxychloroquine (HQ), alternative favipiravir dosages, combination therapy with favipiravir or no comparator), the favipiravir group had significantly improved viral clearance on day 7 after starting therapy (odds ratio [OR] =2.49, 95%, CI=1.19–5.22), but no difference was seen on day 14 (OR = 2.19, 95% CI = 0.69–6.95). Favipiravir accelerates viral clearance by seven days and contributes to clinical improvement in about 14 days [103]. Hassanipour et al. conducted systematic and meta-analysis evaluation to look into the safety and efficacy of Favipiravir in the treatment of COVID-19, which comprised 827 patients. This meta-analysis also found that the favipiravir group had a substantial clinical improvement compared to the control group seven days after hospitalization (RR=1.24, 95% CI: 1.09–1.41). Clinical improvement was 10% higher in the favipiravir group after 14 days of hospitalization, but this difference was not statistically significant (RR=1.10, 95% CI: 0.97–1.25; p=0.108, I2=34.5%, p=0.177) [104].

Current recommendations

However, none of the society and organizational guidelines (IDSA guidelines, the World Health Organization guidelines, National Institutes of Health guidelines) recommends using favipiravir in the management of COVID-19, given the varying results of existing clinical trials data [105]. The Centers for Disease Control and Prevention (CDC) guidance for the clinical care of COVID-19 patients (as of March 2020) emphasizes that there is no specific treatment for COVID-19 and that management should include prompt implementation of recommended infection deterrence and control measures as well as managing complications [106]. At the time of writing, Japan, Russia, Saudi Arabia, Thailand, Kenya and four Indian states, including Maharashtra, had endorsed the use of favipiravir oral medication in the treatment of mild to moderate COVID-19 [107].

Doxycycline

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline class. This drug is a second-generation tetracycline, exhibiting lesser toxicity than first-generation tetracyclines. It is approved for rocky mountain spotted fever, typhus fever and the typhus group, q fever, rickettsial pox, tick fevers caused by rickettsiae, respiratory tract infections caused by mycoplasma pneumoniae, etc. Doxycycline also has a strong anti-inflammatory effect. Elevated levels of blood interleukin (IL)-6 and pro-inflammatory cytokines induced by virally driven hyper-inflammation leading to cytokine storm are one of the most common clinical symptoms of COVID-19 infection. It also suppresses the cytokine storm by lowering pro-inflammatory cytokines (IL-6, IL-8, and tumour necrosis factor (TNF)) [108, 109].

Evidence from *in-silico*, *in vitro* and *in vivo* studies

In silico study discovered that doxycycline suppress the SARS-CoV-2 papain-like protease, which dramatically promotes Egr-1-dependent activation of transforming growth factor-beta 1 (TGF-1) and overexpression of pro-fibrotic responses *in vitro* and *in vivo* in the lungs. Doxycycline has previously been shown to have antiviral effect against the Japanese encephalitis virus, chikungunya virus, dengue virus, and respiratory syncytial virus. *In-vitro* antiviral activity of doxycycline against a clinical isolate of SARS-CoV-2 also showed promise, engaging with the virus at both the entry and post-entry stages. Doxycycline strongly binds to the spike protein (S) of SARS-CoV-2, which is required for viral entry into the host cell as per the docking data. Doxycycline binds to the spike protein via Tyr505 and Arg408 residues. These residues play an important role in connecting with the ACE-2 receptor in the host. Doxycycline found to interact with Mpro, also known as the 3 C-like proteases of SARS-CoV-2, as well as inhibit its RNA-dependent RNA polymerase [110–113]. It exhibits anti-inflammatory effects *in vitro* at low (20–40 mg/day) and high (100 or 200 mg/day) dosages, with inhibitory action on metalloproteases, especially MMP-9, which is likely essential for early viral entry into the cell. Doxycycline also inhibits the production of pro-inflammatory cytokines such as IL-6, IL-8 and TNF [114, 115].

Evidence from clinical studies

In PRINCIPLE trial which was open-label, multi-arm, adaptive platform randomised trial of interventions against COVID-19 in older people (65 years or older, or 50 years or older with comorbidities), who had been unwell (for ≤14 days) with suspected COVID-19 or a positive PCR test for SARS-CoV-2 infection in the community across primary care centres in the UK. Total of 2,689 participants were randomly assigned to usual care only, usual care plus oral doxycycline (200 mg on day 1, then 100 mg once daily for the following six days), or usual care plus other interventions. There was little evidence of difference in median time to first self-reported recovery between the usual care plus doxycycline group and the usual care only group (9·6 [95% Bayesian Credible Interval [BCI] 8·3 to 11·0] days vs. 10·1 [8·7 to 11·7] days, hazard ratio 1·04 [95% BCI 0·93 to 1·17]). The estimated benefit in median time to first self-reported recovery was 0·5 days (95% BCI—0·99 to 2·04) and the probability of a clinically meaningful benefit (defined as ≥1·5 days) was 0·10. Treatment with doxycycline was not associated with clinically meaningful reductions in time to recovery or hospital admissions or deaths related to COVID-19, and should not be utilized as a routine treatment for COVID-19 [116]. Another interventional phase III clinical trial involving 400 individuals, combining ivermectin (6 mg, 2 tablets stat) and doxycycline (100 mg twice daily for five days) was conducted at the Dhaka Medical College in Bangladesh showed promising results [117]. The DYNAMIC study (DoxycYcliNe AMbulatolre COVID-19), was conducted with the aim to check the efficacy of 200 mg doxycycline per day for two weeks. The study showed that combinatorial therapy reduced the meantime to recovery [118].

Current guidelines

In an alert issued by the Department of Health and Social Care (DHSC) on 28 January 2021, stating that azithromycin and doxycycline should not be used in the management of confirmed or suspected COVID-19 [119]. Despite its safety, doxycycline is not suggested for the treatment of COVID-19 patients unless it is used under the direct supervision and guidance of a specialist [119].

Research funding: None
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Yes, all authors state that there is no conflict of interest.
Informed consent: Not required
Ethical approval: No requirement of ethical approval.

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