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Review Article

REPURPOSED DRUGS FOR COVID-19 UPDATE: JANUARY 2021

Author: Kaushal Pant[a]

ABSTRACT:

Early on in the pandemic, many pre-existing drugs and therapies were repurposed for treating COVID-19. In the last one year, some experience has been gained on their efficacy and safety, in the form of case series, retrospective, cohort studies and well powered randomized controlled trials. An online search of published literature and relevant pre-print papers was carried out to ascertain the current status of repurposed drugs and therapies commonly used in the treatment of COVID-19 in India. Trial data is slowly beginning to emerge, some relatively strong, as in the case of Hydroxychloroquine, Remdesivir, Convalescent Plasma, Tocilizumab, Azithromycin and Glucocorticoids, while available literature on other drugs is relatively scanty, often of poor quality and conflicting.

Introduction

SARS-CoV-2has infected more than 100 million people worldwide and claimed more than 2.3 million lives.COVID-19 is primarily a respiratory disease that may progress from the upper respiratory tract to the lungs and thereafter, in some patients, to an uncontrolled systemic inflammation, thrombo-embolism, severe lung damage, respiratory failure, shock and death. The disease is now increasingly recognized to go through broadly three phases with blurred boundaries i.e., mild upper respiratory phase, pulmonary/viral phase and the inflammatory phase. Due to the rapid spread of the pandemic and the resultant morbidity and mortality, already available drugs and therapies have been repurposed for use in COVID-19. It is often difficult to keep track of their current status due to the unprecedented pace of research in this field in the last one year. This brief review aims to search available literature, both published and preprint, in order to assess the current status of these repurposed drugs/therapies.

[a]Senior Specialist, Department of Pulmonary Medicine, ESIC Hospital, Okhla, New Delhi.
Correspondence: kaushalpant@gmail.com

Review

Hydroxy chloroquine (HCQS) was repurposed for the treatment of COVID-19 due to its anti-inflammatory properties and reports of in-vitro activity against SARS-CoV-2[1].

Although early reports in literature werepromising[2,3], the well powered, randomized Solidarity, RECOVERY and ORCHID clearly shown that HCQS has no effect on clinical recovery, initiation of ventilation, duration of hospital stay or overall mortality in patients admitted with COVID-19[4-6]. HCQS has also shown no promise in mild to moderate disease[7,8]. Its emergency use authorization for treating COVID-19 has since been revoked by the Food and Drug Administration, U.S.A. Indian Council of Medical Research (ICMR) however, still recommends its use in early, mild COVID-19 in high-risk patients.

Azithromycin has been shown to have in-vitro activity against RNA viruses as also immuno-modulatory properties[9,10] and due to these reasons, it began to be used along with HCQS in many centers. Published evidence of its use in COVID-19 is scarce. Reports of Azithromycin in combination with HCQS have shown mixed results. Most of them have not shown any benefit either in mortality or viral clearance[11-14]. Two large, prospective, randomized (COALITION I & II) trials have found no benefit of adding Azithromycin to HCQS in mild, moderate or severe forms of COVID-19[15,16]. Recently published results from the RECOVERY trial[17]also shown no benefit of Azithromycin in 2582 admitted patients. In January2021 the PRINCIPLE trial from U.K. also announced that Azithromycin, when given to 526 patients over 50 years within 14 days of onset of symptomsdid not hasten recovery or reduce hospitalizations or deaths. Concerns have also been raised regarding cardiovascular safety when Azithromycin is used with drugs that increase QTc interval such as HCQS[18].

Results from three large randomized trials indicate that addition of Azithromycin to existing standard of care regimens does not appear to improve outcomes. Although other trials are presently assessing the role of Azithromycin in COVID-19 and their results are awaited, current evidence indicates that the use of Azithromycin in COVID-19 should be restricted to only where there is a clear anti-microbial indication.

Ivermectin - an anti-helminthic, shows in-vitro activity against a variety of viruses, including SARS-CoV-2[19]. However, the serum concentration required to inhibit it in vivo has been shown to be practically unattainable in humans[20]. It has also been shown to have anti-inflammatory properties[21].

The first in-vitro study published by Caly et al[19] and the emergence of some small case series spurred the use of Ivermectin worldwide. Association of Ivermectin with improved survival and early recovery in patients with mild, moderate and severe disease has been shown in retrospective studies[22,23]. A retrospective study[24] on patients with mild disease did not however show any benefit. Although a small randomized controlled trial (RCT) did not show any beneficial effect of Ivermectin in mild or moderate COVID-19[25], the results from a large

RCT (preprint) indicate significantly increased rates of early improvement and decreased rates of deterioration in patients with mild/moderate disease who received Ivermectin and Doxycycline[26]. The results however do not specify the number of mild/moderate, hospitalized/non-hospitalized patients in each arm. Another RCT (preprint)did not show any significant benefit of Ivermectin-Doxycycline combination over HCQS-Azithromycin in mild and moderate disease[27]. There are other studies with mixed results that have been posted online but yet to be peer reviewed[28,29]. More than 35 trials are currently investigating its role in COVID-19 as per ClinicalTrials.gov

Overall, there is very little peer reviewed data on Ivermectin and available literature shows mixed results. More prospective, well powered RCT data is awaited. Enthusiasm for the drug is therefore disproportionate to current evidence.ICMR does not recommend the use of Ivermectin in COVID-19 at present.

Doxycycline's use in combination with Ivermectin or HCQS is largely based on its anti-viral and anti-inflammatory properties[31,32]. Currently, there is very little data on its use in COVID-19. Only one published early retrospective case series[32]from New York could be found where Doxycycline, when used alone early in 89 patients with COVID-19 led to reduced hospitalizations and mortality. The results of a trial[26] of Ivermectin-Doxycycline combination have already been discussed above.A randomized trial (preprint) of 116 patients did not show any significant benefit of treatment with Ivermectin-Doxycycline over that with HCQS-Azithromycin combination[27]. Another randomized trial with the same combination on 70 patients, awaiting peer review, demonstrates significant difference in time to recovery but not so in mortality or disease progression when compared to standard of care[28].In January, 2021, the Principle study announced that Doxycycline, when given to 798 patients over 50 within the first 14 days did not hasten recovery or reduce hospitalization. Nine studies using Doxycycline are ongoing at present as per ClinicalTrials.gov.

Lopinavir is an HIV-1 protease inhibitor, which is combined with **Ritonavir** to increase its plasma half-life. Lopinavir is believed to also inhibit the SARS-CoV main protease, which is critical for replication in SARS-CoV-2. It therefore shows in-vitro activity against many coronaviruses, including SARS-CoV-2[37].

Although some observational studies in patients with COVID-19 reported an association of Lopinavir–Ritonavir combination with a shorter duration of viral shedding and fever[34,35], other studies have reported no benefit[36,37]. In a randomized trial of Lopinavir–Ritonavir, hospitalized patients did not show any improvement in viral load, duration of hospital stay or mortality[38].In the RECOVERY trial on 1616 patients admitted to hospital with COVID-19, Lopinavir–Ritonavir was not associated with reduction in duration of hospitalization, risk of progression to mechanical ventilation or death[39]. Interim results from the Solidarity trial on 2062 patients further substantiated these findings[4]. The debate around the use of this combination is therefore more or less settled.

Favipiravir is an antiviral drug that selectively inhibits

the RNA-dependent RNA polymerase of influenza viruses and is approved for novel Influenza virus infections in Japan. It also acts in-vitro against many other RNA viruses, including SARS-CoV-2[40]. However, high concentrations of Favipiravir are required to reduce SARS-CoV-2 infection in Vero cells[41].

In May 2020, a poorly designed, open-label, non-randomized, comparative study from China[40] reported reduction of viral load and improvement in radiological findings in 35 COVID-19 patients who were administered Favipiravir, when compared to 45 patients who received Lopinavir-Ritonavir. Thereafter, in a prospective, open label randomized trial without a control arm, Chen et al[41] (preprint) reported that clinically confirmed patients given either Favipiravir or Umifenovir have similar clinical recovery rates. An observational study on Favipiravir was also started in Japan and its preliminary report in hospitalized patients showed positive results[44]. However, two recent prospective randomized trials[45,46], one of them Indian, do not show any effect on viral clearance in patients who received Favipiravir while another one[47] did. Around 40 trials (ClinicalTrials.gov) on Favipiravir are ongoing. Only one of them has posted results that show early improvement in clinical status in patients receiving Favipiravir. The scanty and predominantly poor quality of available literature and current evidence from RCT data therefore does not justify its widespread use.

Remdesivir was first developed by Gilead Sciences for treating RNA viruses that had global pandemic potential. It was subsequently used in outbreaks of Ebola, MERS and SARS with mixed results. Its ability to inhibit SARS-CoV-2[33]prompted its use widely on compassionate grounds.

Two double-blind, placebo-controlled RCTs using Remdesivir were initiated in Chinain February 2020, one on patients with mild and moderate disease(since suspended), and another on patients with severe COVID-19[48].In February 2020, the National Institute of Allergies and Infectious Diseases initiated the Adaptive COVID-19 Treatment Trial (ACTT-1) [49], a double-blind, RCT to evaluate Remdesivir in COVID-19. In early May, Gilead Sciences initiated two more, SIMPLE trials[50,51].TheRCT from China[48] reported that Remdesivir did not significantly reduce the time to clinical

improvement, time to viral clearance or reduce mortality in patients with severe COVID-19.In the SIMPLE trial on moderate disease, patients with SPO2>94% randomized to a 5-day course of Remdesivir showed a significant difference in clinical improvement compared with standard care[50]. There was however no reduction in 28 days mortality. The other SIMPLE trial on patients with severe COVID-19did not show a significant difference between a 5-day and a 10-day course[51]. The ACTT-1 trial[49]reported that those patients who received Remdesivir recovered significantly more quickly (by 5 days) than those who received placebo. Benefit was more in patients receiving low flow oxygen and not much in those receiving NIV and definitely not in those receiving invasive ventilation. Remdesivir however did not reduce mortality at 28 days. Recently, Remdesivir plus Baricitinib (an oral, selective inhibitor of Janus kinase 1 and 2, used to treat Rheumatoid Arthritis) have been reported to be superior to Remdesivir alone in reducing recovery time, notably among patients

receiving high-flow oxygen or non-invasive mechanical ventilation[52].The Solidarity trial has however demonstrated that there was little or no change in outcome as indicated by overall mortality, initiation of ventilation, and duration of hospital stay, in2743 admitted patients who received Remdesivir. As a result, recently, The WHO Guideline Development Group has advised against its use in COVID-19.

The current evidence therefore shows lack of mortality benefit of Remdesivirin COVID-19, although patients who receive it and survive may recover more quickly. It also seems that there is no significant efficacy difference between a 5 and a 10 days regimen. Remdesivir may yet have a role in some subsets of patients when combined with other drugs like glucocorticoids, other inflammatory drugs and monoclonals antibodies etc.

Glucocorticoids have been widely used in syndromes closely related to that seen in Covid-19, like in SARS,MERS and influenza infections due to their anti-inflammatory and immunosuppressive properties. There is however no clarity regarding their precise role in these conditions due to lack of data from sufficiently powered RCTs.

To begin with, there was similar uncertainty about their therapeutic role in COVID-19[53]. An interim guidance from WHO released in May, 2020 also cautioned against its use. However, clinicians around the world began to use glucocorticoids in severe cases of COVID-19 due to their beneficial effects in ARDS, with mixed results[54,56]. The first prospective, but partially randomized, open label trial (preprint) reported a significantly decreased risk of adverse outcomes in 56 patients with moderate-severe Covid-19 who were given Methylprednisolone for 6 days[57]. In the landmark, controlled, open-label RECOVERY trial[58] on hospitalized patients with COVID-19, significantly more patients died in the usual care group (n=4321) than in the dexamethasone group (n=2104) within 28 days of randomization. Mortality was significantly lower among patients receiving invasive mechanical ventilation or oxygen but not among those (with the possibility of harm) who did not need oxygen. These favourable findings were also supported by three other trials including the REMAP-CAP trial, which stopped enrolment when the RECOVERY trial results were released[59,61]. A meta-analysis[62] of 7 RCTs with 1703 patients with minimal heterogeneity across studies, confirms the reduction in 28-day mortality with the use of glucocorticoids. A recent Brazilian double-blind, randomized, placebo-controlled trial has however reported no 28 days mortality benefit of treatment with methyl-prednisolone[63]. In this trial the duration between disease onset and randomization was 13 days and the duration of therapy was 5 days and that may have affected outcomes.

Overall, there is strong trial evidence to support the use of glucocorticoids in patients hospitalized with COVID-19 who require oxygen or ventilation. The RECOVERY trial suggests that it may be harmful if given to patients who do not need oxygen. Although 6mg of dexamethasone was used in the RECOVERY trial, glucocorticoids have been used in varied forms, doses and durations. There is still uncertainty about the optimum timing, dose and duration of glucocorticoid therapy and more detailed studies could help answer these questions.

Low Molecular Weight Heparins (LMWH) not only have an anticoagulant and anti-inflammatory action but also inhibit viral entry into host cells[64].

They are being used widely in patients with COVID-19 due to the high incidence of pulmonary and extra-pulmonary thrombo-embolic complications in these patients. Patients often exhibit raised serum levels of D-dimer, fibrinogen, fibrinogen degradation products and Factor VIII. High level of D-dimer on admission has also been shown to be associated with increased risk of thrombo-embolism and mortality[65,66]. As a result, LMWH have been recommended in COVID-19 by many organizations worldwide, some recommending only prophylactic doses[65,67], while others recommending intermediate or therapeutic doses in high risk patients[68,69]. Trial evidence, however, is still based only on a very few observational and retrospective studies.

Anticoagulation has been shown in many retrospective studies to be associated with lowering of D-Dimer levels, lower risk of ICU admission and significantly lower mortality, especially in patients with a markedly high serum D-dimer level or a high sepsis-induced coagulopathy score. The incidence of major bleeding is generally low, being slightly higher in those patients receiving therapeutic doses. [70,72].

There is very little data comparing different levels of anticoagulation dosing in patients of COVID-19. Both intermediate and therapeutic dosing have shown more benefit than prophylactic dosing without any excessive risk of bleeding in two retrospective studies as well as one small, randomized open label trial[73,75].

Although the certainty of evidence is low, anticoagulation continues to be recommended in patients with COVID-19 who require oxygen or ventilation. There is currently insufficient trial data to recommend the routine use of intermediate or therapeutic doses of heparin-based regimens for thromboprophylaxis in even high-risk patients. The risk of bleeding with LMWH is low, being slightly more with therapeutic doses.

Convalescent Plasma (CP) from recovered patients contains neutralizing antibodies that are produced as a result of host immune response. CP may not only modulate the immune response but also exert an anti-inflammatory effect[76].

CP has been used in the past to treat many viral diseases with varying degrees of success. Therefore, very early on in the pandemic, it was suggested as a potential treatment choice[76] and CP therapy received approval for use in several countries, including India. Early studies began to report an association of CP with improvement in clinical outcomes and it was also found to be safe[77,78]. Subsequently, two randomized trials found no benefit in mortality or early clinical improvement with CP therapy[79,80]. In the Chinese study[79] the time to randomization was 30 days while in the ConCOVID study[80], 79% of the enrolled patients already had neutralizing antibodies. It was suggested that CP may benefit patients with recent onset of symptoms, who do not yet have antibodies to SARS-Cov-2. A preliminary report[81] (preprint) of 35322 patients from an expanded access programme in the U.S. demonstrated the relationships between reduced mortality and earlier time to transfusion and higher antibody levels in donor plasma. Two small RCTs (preprints) have supported these

findings[82,83]. However, the limited number of events in the control group prevents drawing firm conclusions about CP efficacy from one of these trials.

A large, real life, RCT (PLACID trial) from India[84]did not demonstrate any reduction in28-day mortality or progression to severe disease in patients with moderate disease who received CP. The level of neutralizing antibodies in CP did not affect outcomes. However, as with the ConCOVID study, 83% of patients had detectable neutralizing titer at the time of enrolment. Recently, in a double blind, placebo controlled (PlasmAr) trial[85]the median titer of anti–SARS-CoV-2 IgG level was 1:50 in the 228 enrolled patients and 46.0% of patients had no detectable antibody level. The infused CP had a median titer of 1:3200 of SARS-CoV-2 antibodies and the median time to enrolment was 8 days. No significant differences was observed in clinical status or mortality between patients treated with CP and those who received placebo in this trial. In a recent RCT[86] on 80 patients older than 65 years with mild COVID-19,administration of CP with titer of anti-SARS-CoV-2 IgG greater than 1:1000 within 3 days of onset of symptoms reduced the risk of progression to severe disease by 48%. The study was however not sufficiently powered to assess its effect on mortality. In January 2021, Joyner et al[87] reported that among patients with COVID-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. In January 2021, the REMAP-CAP trial announced that CP therapy did not improve outcomes in 912 severely ill COVID-19 patients. Recruitment for patients with moderate disease is however still ongoing. Similarly, in January 2021, the Recovery Group announced that preliminary data on 10,406 randomized patients shows no benefit of CP therapy on 28 days mortality.

Although there is substantial evidence at present that CP therapy may not benefit patients with COVID-19 and doubts have been raised about its safety[88], the role of immune plasma when given very early in certain sub-group of patients needs further exploration. After the PLACID trial, ICMR has recently revised its advisory on the use of CP in COVID-19.

Tocilizumab (TCZ) is a humanized anti-interleukin-6 receptor monoclonal antibody used to treat severe Rheumatoid Arthritis and CART cell therapy induced cytokine storm. It inhibits Interleukin-6 (IL-6) signaling by binding to IL-6 receptor and was therefore suggested as a possible treatment option for COVID-19[89]. Increase in serum levels of various pro-inflammatory cytokines, including IL-6, is associated with pulmonary inflammation and extensive lung damage in COVID-19. IL-6 has been shown to play a central role in cytokine storm. High levels of IL-6 are associated with severe disease and increased risk of mortality in COVID-19[90]. Early data from 13 retrospective case-control and 6 retrospective single-armed studies shows that TCZ use was associated with a lower rate of admission to ICU, lesser use of ventilation and lower mortality[91].However, in an open-label RCT on 130 patients requiring oxygen[92], TCZ did not reduce 28 days mortality. Dexamethasone was however used more in the control group, which may have mitigated the treatment effect.

In the first randomized, double blind, placebo-controlled trial (COVACTA, preprint)[93] on 438 COVID-19 patients who required oxygen, TCZ did not improve clinical status or reduce mortality. Recently, a similar trial[94] involving 242 patients with a hyper-inflammatory phenotype also found TCZ to be ineffective in preventing intubation or death. In an open label RCT[95] similar outcomes were found in 123 patients with an inflammatory phenotype requiring oxygen. The fact that 14 out of 63 patients in the standard arm received TCZ, may have however confounded mortality data in this study. In a recent open label randomized trial[96] on 65 patients who were either on oxygen or on mechanical ventilation in the last 24 hours with severe or critical covid-19, TCZ did not improve clinical outcomes at 15 days. The phase III EMPACTA study group[97] reported in January 2021 that in patients with SPO2<94% but not on any form of ventilatory support, TCZ and standard care reduced the likelihood of progression to the composite outcome of mechanical ventilation or death when compared with placebo and standard care, but there was no difference in incidence of death from any cause between the two groups.

The REMAP-CAP international platform trial[98], has also reported in January 2021, that patients with Covid-19 receiving high flow nasal oxygen, invasive or non-invasive ventilator support or cardiovascular organ support in intensive care, treatment with TCZ (n=366)along with standard of care, improved outcomes, including survival. Standard of care included Glucocorticoids in more than 80% of these patients.

Although published RCT data is generally disappointing with respect to survival and enthusiasm for TCZ has declined over time, recent reports have rekindled interest in it. Subgroups of patients may yet be identified in whom TCZ may be helpful. One consistent result across all trials to date is that no increase rates of serious adverse events, including infections, have been reported.

Conclusion

Trial evidence strongly supports the use of glucocorticoids in hospitalized patients who require oxygen or any form of ventilation and it is the only drug that reduces mortality in COVID-19. Remdesivir has been shown to have no mortality benefit in COVID-19 in well powered controlled trials, although it may

hasten recovery in those who survive. There is strong evidence that Hydroxychloroquine and Lopinavir-Ritonavir combination do not either hasten recovery or reduce mortality in COVID-19. Well powered RCT data suggests that Azithromycin also does not improve outcomes in COVID-19. The available data on Favipiravir, Ivermectin and Doxycycline is sketchy, mostly of poor-quality and conflicting and does not justify their continuing use. Most of current evidence suggests that CP therapy and TCZ may also be ineffective in reducing mortality or disease progression in COVID-19.Their role in certain sub-group of patients however needs further exploration. LMWH are recommended by organizations worldwide in patients with COVID-19 who require oxygen or/and ventilation because retrospective studies have shown that their use reduces ICU admissions and improves survival. There is however not enough trial data at present to substantiate this practice.

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