ANTIVIRALS

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Introduction

Antivirals may be viewed by some as anti-infective agents; but they do have a role in immunomodulation against all stages of COVID-19. They can be part of medications given starting from the early stage of infection until the later stage of hyper-inflammation and systemic involvement. As a study on SARS-CoV also suggested, the peak inflammatory cytokine (IL-6 and IL-8) levels concurred with, or after the peak viral load, and preceded or concurred with the maximum pulmonary infiltrates. Thus, it is probable that viral replication leads to the activation of proinflammatory cytokines that, together with other factors, contribute to disease progression.[1]

Antiviral agents have also been included in large multicenter, international clinical trials. However, the adaptive quality of these studies enables them to discontinue a certain drug if there is no evidence of beneficial effects. Such is the case for the removal of lopinavir/ ritonavir in the in the World Health Organization's "Solidarity Trial", RECOVERY Trial in the United Kingdom, ASCOT trial in Australia, and the ACTT trial by NIAID. Furthermore, preliminary results from various studies and systematic review and meta-analysis have been published since the last version of this document.

a. FAVIPIRAVIR / T-705/ FAVIPIRA/ FAVILAVIR

Introduction

Favipiravir is approved for treatment of novel influenza on February 15, 2020 in China and is currently undergoing clinical trials in treating COVID-19.[2]

Since the last edition of this paper, a number of studies have emerged with promising results. Several countries, including China, India and Russia, have now approved its use for COVID-19.

Mechanism of Action

In an vitro study on SARS-Cov-2, favipiravir acts as a nucleoside analogue inhibiting the RNA-dependent RNA polymerase of the SARS-CoV-2 causing chain termination, slowed RNA synthesis and lethal mutagenesis. This causes decreased viral replication may possibly prevent excessive release of proinflammatory cytokines.[3]

Clinical Trials

A preprint of a randomized open-label clinical trial comparing favipiravir and arbidol showed no significant difference between the 2 groups in terms of clinical recovery rate at 7 days from the beginning of treatment. For the secondary outcomes, the time to fever and cough relief in the favipiravir group was significantly shorter than that in the Arbidol group (P<0.0001). One limitation of this study is the diagnosis of COVID-19 without virologic tests. As such, included patients may have pneumonia due to other pathogens.[4]

An open-label non-randomized study in China comparing favipiravir + interferon-a inhalation and LPVr + interferon-a inhalation showed that patients in the favirapir group had significantly shorter viral clearance time compared to the LPV/r group (P < 0.001). There was no significant difference in the improvement rates of chest CT changes after days 4 and 8 of treatment; but the improvement rates after day 14 in the FPV arm were significantly higher than those in the LPV/r arm (91.4% versus 62.2 %, 32/35 versus 28/45, P = 0.004) [5]

A phase 3 clinical trial in India involving 150 patients with mild to moderate COVID-19 demonstrated faster viral clearance in the favipiravir group compared to the control group (Hazard Ratio 1.367 [95%CI 0.944,1.979]; p=0.129). Moreover, there was 40% faster achievement of clinical cure at 3 days (HR 1.749 [95% CI 1.096, 2.792]; p=0.029). A statistically significant “clinical cure” at 69.8% in 4 days, versus the standard supportive care group (44.9%) was reported. Among patients who deteriorated and required O2 support, those receiving favipiravir had a longer median time of use of oxygen of 5 days (95%CI 1.0,6.0) vs 2 days (95% CI 1.0-4.0) for those who received standard care. Adverse events (AEs) were reported in 26 patients in the favipiravir treatment arm (35.6%) as compared to six patients in the control arm (8%) however, most AEs were mild to moderate and none led to drug discontinuation or dosing adjustments. This study is not yet published and has not undergone peer review.[6]

There are 43 ongoing registered studies on favipiravir for COVID-19, including pharmacokinetic studies and 1 study on its possible prophylactic use. (Appendix 6-A)

Recommended dose

1600 mg 2x a day on day 1, then 600 mg 2x a day on days 2 to day 14, was used in a Chinese open label control study using favipiravir for moderate COVID-19 patients [5]

1800 mg 2x a day on day 1, then 800 mg 2x a day on day 2 onwards for a maximum of 14 days, was used in Glenmark’s phase 3 clinical trial of favipiravir in patients with mild to moderate COVID-19.[6]

Adverse Effects

Some of the adverse effects are raised serum uric acid, abnormal liver function tests, psychiatric symptom, GI disturbance. Most were mild to moderate and transient. It is contraindicated for known or suspected pregnant women and lactating women [5, 7]

Drugs that may potentially cause drug interactions with favipiravir are aldehyde oxidase inhibitors such as selective estrogen receptor modulators (raloxifene, tamoxifen, estradiol), H2 receptor antagonist (cimetidine) calcium channel blockers (felodipine, amlodipine, and verapamil), anti-arrhythmic drugs (propafenone) and tricyclic antidepressant amitriptyline.[8]

b. LOPINAVIR/RITONAVIR (LPV/r)

Introduction

A protease inhibitor used as an antiretroviral treatment in combination with other antiretroviral agents for HIV 1 in adults and pediatric patients.[9] The updated guidelines of the Infectious Disease Society of America (IDSA) and the National Institutes of Health (NIH) for the management of COVID-19 recommends the use of LPV/r in hospitalized patients only in the context of a clinical trial.[10, 11] The Surviving Sepsis Campaign (SSC) guideline suggests against the use of LPV/r in critically ill adults.[12] The WHO interim guidance, Australian and New Zealand Intensive Care Society (ANZICS) guideline and National Institute for Health and Care Excellence (NICE) guideline did not address the use of LPV/r in COVID-19.[13]

On 4 July 2020, WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's hydroxychloroquine and lopinavir/ritonavir arms. These interim trial results show that hydroxychloroquine and lopinavir/ritonavir produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care. Solidarity trial investigators will interrupt the trials with immediate effect. For each of the drugs, the interim results do not provide solid evidence of increased mortality. [14]

Mechanism of Action

Lopinavir has in vitro inhibitory activity against SARS-CoV. It also blocks a post entry step in the MERS-CoV replication cycle.[9,15] Ritonavir is used in combination with lopinavir to increase the half-life through the inhibition of cytochrome P450.[15] Protease inhibitors prevent cleavage of the viral polyproteins resulting in the formation of non-infectious viral particles.[2]

All protease inhibitors increase the release of Macrophage Inflammatory Protein 1α (MIP-1a) and Monocyte Chemotactic Protein-1 (MCP-1) that function to recruit cells of the innate immune system.[16]

Clinical Studies

In a randomized, open-label, multi-center study involving a total of 127 patients, there was no difference in the time to clinical improvement for patients with severe COVID-19 who received LPV/r and standard of care compared to standard of care alone, in the intention to treat analysis (clinical improvement hazard ratio 1.31; 95% CI 0.95 to 1.80).[17] A study correlating viral clearance and blood biochemical index of 94 discharged patients showed no significant difference on the average length of hospital stay nor PCR negative conversion times–among adult COVID-19 patients treated with LPV/r-IFN-α (N=46) and ribavirin-LPV/r + IFN-α combination (N=21). This study though, had a small sample size.[18]

An exploratory randomized study done in China involving 86 patients showed that the mean time for positive-to-negative conversion were not statistically different in the LPV/r group, the arbidol group and the control group (p=0.981). There was no statistically significant difference in the rates of conversion after 7 days, 14 days and 21 days.[19]

On June 30, 2020, the RECOVERY trial found no benefit with lopinavir-ritonavir in COVID-19 and stopped randomization to that arm. A total of 1596 patients were randomized to lopinavir-ritonavir and compared with 3376 patients randomized to usual care alone. At the start of the trial, 4% required invasive mechanical ventilation, 70% required oxygen alone, and 26% did not require any respiratory intervention. The Independent Data Monitoring Committee recommended unblinding of results to the investigators and they found no significant difference in the primary endpoint of 28-day mortality (22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; p=0.58). The results were consistent in different subgroups of patients. There was also no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay. They had difficulty administering the drug to the mechanically ventilated patients, so they could not make conclusions on its effectiveness in this group of patients.[20]

The AustralaSian COVID-19 Trial (ASCOT) also removed the hydroxychloroquine and lopinavir/ritonavir arms of the trial, following the statement issued by the WHO together with the RECOVERY trial.[21]

As of July 6, 2020, there are 41 registered clinical trials investigating LPV/r for its use in COVID-19 management, while 4 trials were terminated. (Appendix 6-B)

Recommended Dose

Adult dose: 400mg/100 mg twice a day for 10days[22] or 14 days[17].

Pediatric dose: 7-15kg: 12mg/3mg/kg; 15-14kg: 10mg/2.5mg/kg; >40kg: as adult

dose as used in clinical trials for COVID-19.

Doses to be taken twice a day for 1–2 weeks.

Adverse Effects and Drug Interactions

Adverse events observed among patients taking LPV/r for COVID-19 were gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal discomfort.[17] It may also cause hepatotoxicity, pancreatitis & ECG abnormalities.

Drug interactions are common with LPV/r due to their inhibition of cytochrome P450 that may result in increased plasma concentrations of other co administered drugs, consequently, leading to the therapeutic and adverse effects as well. Drugs that are contraindicated for use with LPV/r include alpha-1 adrenergic agonists (alfuzosin, prazosin, tamsulosin), neuroactive drugs (midazolam, triazolam, phenobarbital, phenytoin, carbamazepine), drugs for cardiovascular conditions (amiodarone, bepridil, flecainide, propafenone, quinidine, dronedarone, sildenafil), cholesterol lowering agents (lomitapide, lovastatin, simvastatin), antimicrobials (rifampicin, itraconazole, ketoconazole, metronidazole, elbasvir/grazoprevir), antihistamine terfenadine & astemizole, fluticasone, colchicine, ergot derivatives, ethinyl estradiol/ norethindrone acetate.[23, 24]

c. OSELTAMIVIR

Introduction

Oseltamivir is a viral neuraminidase inhibitor used for the treatment and prophylaxis of Influenza A, H1N1 Influenza A and Influenza B for both the pediatric and the adult population.[25] It was used widely during the initial phase of the COVID-19 outbreak in China because of concurrent peak influenza season. A large proportion of patients received empirical oseltamivir therapy until the discovery of SARS-CoV2.[26] In Egypt, Oseltamivir is included in their standard of care treatment for confirmed COVID-19 patients.[27]

Mechanism of Action

Oseltamivir is a potent and selective inhibitor of influenza virus neuraminidase enzymes. Inhibiting the neuraminidase enzyme reduces viral shedding and infectivity by hampering the viral entry into uninfected cells, the release of recently formed virus particles from infected cells and further spread of the virus.[25] An initial in vitro study on COVID-19 inferred oseltamivir, combined with other antivirals lopinavir and ritonavir, may be highly effective against COVID-19 and suggested further investigation.[28]
However, recent in vitro studies showed oseltamivir to have no antiviral effect against COVID-19.[29, 30]

Clinical Trials

The WHO interim guidelines on clinical management of suspected COVID-19, has no recommendation on the use of oseltamivir. It has no role in the management of COVID-19 once influenza has been excluded.[31, 32] A retrospective, single center case series of the 138 consecutive hospitalized patients in Wuhan, China, in which most of the patients received oseltamivir, reported that no positive outcomes were observed after receiving antiviral treatment with oseltamivir.[33]

Several clinical trials are still evaluating the effectiveness of oseltamivir in treating SARS-CoV-2 infection, mostly in combination with other antivirals and medications.

As of this writing, there are 13 registered clinical trials involving oseltamivir in COVID-19, with 7 trials presently recruiting subjects. To date, preliminary results are not yet available for these clinical trials.

Recommended dose

300 mg PO per day for 10-14 days used in a clinical trial for COVID-19 in Bangkok[34] or 75 mg PO every 12 hours for 5-10 days[27] as used in Egypt's treatment guideline for COVID-19.

Adverse Effects

Oseltamivir adverse effects reported are nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children.[35]

d. REMDESIVIR/ RDV/ GS-5734

Introduction

It is an investigational drug with broad-spectrum activities against MERS and SARS in vitro and has been tested for Ebola.[36] It is currently being investigated in clinical trials and is also available through expanded access and compassionate use for certain patient populations.

The NIH updated their revised recommendation in the COVID-19 treatment guidelines on July 24, 2020 stating that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO (BI), and recommends its use for 5 days or until hospital discharge, whichever comes first (AI). However there is uncertainty regarding whether starting remdesivir confers clinical benefit in patients with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO.[11]

Mechanism of Action

Remdesivir, a nucleotide analog drug that needs to be converted into its active triphosphate form, inhibits the SARS-CoV-2 RNA dependent RNA polymerase (RdRp) activity, terminating its replication and subsequent decrease in viral RNA production.[31]

As the SARS-CoV study stated that it is probable that viral replication leads to activation of the pro-inflammatory cytokines, decrease in viral replication may possibly modulate the production of pro-inflammatory cytokines.[1]

Clinical Trials

Remdesivir is included in the WHO SOLIDARITY Trial for the treatment of COVID-19. Phase III trials are underway to evaluate the efficacy and safety of remdesivir in patients with mild or moderate and severe COVID-19 respiratory disease.

A study analyzed data from 53 patients who were given remdesivir for compassionate use and it showed that 68% of patients had improvement in terms of oxygen support, 18 days after receiving the first dose [37]

In a randomized, double-blind multicenter placebo-controlled trial of 237 severe COVID-19 patients, remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]). However, the trial did not attain the predetermined sample size of 452 subjects because the outbreak of COVID-19 was brought under control. [38]

A preliminary report from The Adaptive COVID-19 Treatment Trial (ACTT) sponsored by the NIAID indicated that patients who received remdesivir had a 31% faster time to recovery than those who received placebo. The median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group.[39] This study has been completed but final results are not yet available.

In a randomized, open-label, phase 3 trial of 397 COVID-19 patients, it evaluated the safety and efficacy of both 5-day and 10-day dosing durations of remdesivir in patients with severe COVID-19. Sixty-five percent (65%) of patients who received a 5-day course of remdesivir showed a clinical improvement at day 14. As a comparison, 54% of patients received a 10-day course. After adjustment for imbalances in baseline clinical status, patients receiving a 10-day course of remdesivir had a distribution in clinical status at day 14 that was similar to that of patients receiving a 5-day course. A post-hoc analysis in terms of oxygen support status showed 40% (10 of 25) in the 5-day group had died by day 14, as compared with 17% (7 of 41) in the 10-day group[40] With the lack of randomization and no placebo control, however, the magnitude of benefit cannot be determined.

A preliminary report from an open-label study, this time with a control group, evaluated the safety and efficacy of 5-day and 10-day dosing regimens of remdesivir, compared with standard of care alone, in patients with moderate COVID-19. Initial results of the study demonstrated that patients in the 5-day remdesivir treatment group were 65 percent more likely to have clinical improvement at Day 11 compared with those in the standard of care group (OR 1.65 [95% CI 1.09-2.48]; p=0.017). The odds of improvement in clinical status with the 10-day treatment course of remdesivir versus standard of care were also favorable, trending toward but not reaching statistical significance (OR 1.31 [95% CI 0.88-1.95]; p=0.18). No new safety signals were identified with remdesivir across either treatment group.[41] This study will still have to be submitted for publication.

As of July 27, 2020, there are 19 registered clinical studies on remdesivir, with 10 studies, currently recruiting patients. (Appendix 6-C)

Recommended dose

Adult Dose: 200 mg loading dose on day 1 followed by 100 mg IV once-daily for 4 to 9 days as used in clinical trials for COVID-19.

Pediatric doses of remdesivir are used in patients with Ebola.[2] No data for use in pediatric COVID-19 patients.

Adverse Effects

Common adverse events in COVID-19 patients were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. Adverse events were more common in patients receiving invasive ventilation. [37]

According to Goldman JD, et al, the most common adverse events were nausea (9%), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).[40]

e. RIBAVIRIN/RBV

Introduction

Ribavirin is a broad-spectrum antiviral drug that hinders viral replication and spread.[42] It is primarily used for Respiratory Syncitial Viral infection, Influenza virus and chronic Hepatitis C.[1, 36] A study on patients with SARS treated with LPV/r and ribavirin had a lower risk of ARDS and death compared with monotherapy.[43] Most published international recommendation guidelines for the treatment of COVID-19 have not included ribavirin in their reports on treatment for COVID-19.[13]

Mechanism of Action

In a review of nucleotide inhibitors, RBV was found to cause human Coronavirus eradication in vitro.[44] For SARS patients, it is effective as prophylaxis and as treatment when combined with IFN-b.[45] Ribavirin has also been found to reduce macrophage activation, diminish Th2 cytokine production and preserve Th1 cytokine production among patients with hepatitis C virus.[46]

Clinical Trials

Ribavirin is presently included in the general treatment of COVID-19 in Chinese treatment guidelines[22]

No significant difference on average lengths of hospital stay nor PCR negative conversion times were observed among adult COVID-19 patients treated with LPV/r-IFN-α and ribavirin-LPV/r -IFN-α combination.[18]

A multicenter, prospective, open-label, randomized, phase 2 trial in adults with COVID-19 was done in Hong Kong that evaluated the safety and efficacy of ribavirin combined with LPV/r + interferon. The control group received LPV/r only. The median number of days from symptom onset to start of study treatment was 5 days; the primary outcome was time to achieve a negative RT-PCR. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days) than the control group (12 days) with a hazard ratio of 4.37 ([95% CI 1.86–10.24], p=0·0010). Adverse events included self-limited nausea and diarrhea with no difference between the two groups. Early triple antiviral therapy was safe and superior to LPV/r alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19.[47]

There are 5 registered clinical trials, with 2 of which are currently recruiting. (Appendix 6-D)

Recommended dose

500 mg intravenous infusion for adults 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir for not more than 10 days.[22]

Adverse Effects

Ribavirin can reduce hemoglobin concentration.[1] It is contraindicated in patients with severe hepatic and renal impairment and in known or suspected pregnant women.[48]

f. UMIFENOVIR (ARBIDOL)

Introduction

This is used for prophylaxis and treatment of influenza A and B viruses and other human pathogenic respiratory viruses. It is only available in China and Russia.[49]
China has added Umifenovir as an antiviral option in their treatment protocol for COVID- 19.[50]

Mechanism of Action

Umifenovir has also been reported to produce an immunomodulatory response by inducing interferon production and stimulating the phagocytic function of macrophages.[43] Umifenovir prevents the fusion of the viral membrane with the endosome after endocytosis.[49]

In vitro studies on umifenovir showed that it can bind lipid membranes and may alter membrane configuration of the cytoplasm or the endosome, which are crucial for viral attachment and fusion. These results suggested that umifenovir impeded not only viral attachment, but also release of SARS-CoV-2 from intracellular vesicles.[30]

Clinical Trials

A systematic review and meta-analysis on the efficacy and safety of umifenovir for COVID-19 involved 12 studies with a total of 1052 patients. It showed no significant difference of conversion time from positive to negative SARS-COV-2 nucleic acid via PCR between the umifenovir vs the control group. The umifenovir group was not associated with a higher negative rate on day 7 (RR:1.09; 95% CI: 0.91 to 1.31), however showed increase negative rate on day 14 (RR:1.27; 95% CI 1.04 to 1.55). Umifenovir was also not associated with the incidence of critically ill patients and death. Furthermore, this meta-analysis showed no significant association between umifenovir and symptom alleviation of cough and fever on day 7, and length of hospital stay. This drug was also found to be safe among patients with COVID-19.[51] The limitation of the said meta-analysis was the low quality and certainty of evidence and heterogeneity of the studies included. However, several ongoing clinical trials evaluating efficacy of umifenovir for COVID-19 may clarify this issue.

At the time of writing, there are a total of 14 ongoing registered clinical study for umifenovir in COVID-19 patients. One study in China involving 86 COVID patients was completed, with official results still to be published. (Appendix 6-E)

Recommended dose

200mg PO, 3 times a day, for not more than 10 days.[22]
Pedia: 10 mg/kg/d tid for <50 kg; 0.6 g/d tid for ≥50 kg[32]

An in vitro study suggested that umifenovir is potentially effective to treat COVID-19 patients, however the current recommended dose by the Chinese Guidelines may not be able to achieve the ideal therapeutic efficacy to inhibit SARS-CoV2 infection and should be increased.[30]

Adverse Effects

Umifenovir was shown to be safe, even for use in pregnant women and showed no teratogenic effect. Combination LPVr + umifenovir induced liver damage in about 50% of treated patients.[52] The usage over several days to one month was also well tolerated. Some of the reported side effects are diarrhea, dizziness, jaundice and elevated serum transaminase, occasional bradycardia.[49]

CONCLUSION FOR THE SIX ANTIVIRALS DISCUSSED

Antivirals may also have an immunomodulatory role for COVID-19 cytokine storm. More biomolecular studies have to be done to establish this effect.

Even with the increasing number of published studies, convincing evidence of significant benefit does not exist yet for any antiviral treatment. Different countries may have adapted their own treatment guidelines; nonetheless, a unified recommendation for the use of any antiviral medication is still needed.

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