AUGUST 2020 / VOLUME 10 / ISSUE 2

BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL COLLEGE & GENERAL HOSPITAL

DEPARTMENT OF PHARMACOLOGY,

LTMMC & LTMGH, Sion, Mumbai – 22.

Committee Members for Bulletin on Adverse Drug Reactions

INDEX

From the Editor's Desk . . . . ✍

Dear Readers,

Currently, the whole world is struggling to contain and overcome the COVID-19 pandemic. With no definitive and proven treatment options, the challenges have doubled. The literature on COVID-19 is evolving day by day. In view to provide a brief overview of the same, we have dedicated this issue to treatment and safety updates regarding the same.

Our two review articles will provide readers an overview of pharmacotherapeutic options for the treatment of COVID-19 and developments related to candidate vaccine for SARs-COV2. For this issue instead of a case report, we have incorporated the highlights of the WHO report of descriptive analysis of COVID -19-related spontaneous from VigiBase. We have also included new drug approvals, safety alerts related to these drugs and interesting puzzles and crosswords based on COVID-19.

Finally, I would like to thank all the clinical departments from our institute for their valued contribution to Pharmacovigilance and to the authors for contributing. With immense pride and privilege, I would also like to thank all the members of the Department of Pharmacology for their efforts in bringing out the current issue of this publication.

Thank you,

Dr. Sudhir Pawar

PHARMACOTHERAPY OF COVID-19

Dr. Vidisha Parulekar*, Dr. Giridhar**

**Speciality Medical Officer, ** First year Resident*
Department of Pharmacology, LTMMC & GH, Sion, Mumbai

Abstract

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread globally despite unprecedented social isolation and restrictions resulting in widespread economic decline. To date, no treatments have been definitively shown to be effective; however, a multipronged approach to mitigate transmission, morbidity, and mortality is ongoing. With the rapid transmission of disease, even the off-label use of available therapies has been impeded by limited availability. Several antivirals, antimalarials, and biologics are being considered for treatment at this time.

Keywords:

Antivirals, Remdesivir, Favipiravir, immunomodulators

Introduction

Since the first case of Covid-19 was discovered in China in December 2019, currently 96,052,536 infected cases have been reported across the globe [1]. Though being predominantly a mild disease, 1-2% of the population is known to face its severity [1]. Hence, attempts are needed towards therapeutic advancements to tackle these subsets of patients. In this review, we will be covering drugs currently being used in the treatment of COVID-19 excluding nutritional supplements and drugs under evaluation.

I. Antivirals

Antivirals are agents proposed to eradicate the coronavirus or at least reduce the effects and hinder the contagion of the SARS-CoV-2. Many groups such as protease inhibitors, broad-spectrum antivirals, RNA-dependent RNA polymerase inhibitors, nucleoside and neuramidase inhibitors, and polymerase acid endonuclease inhibitors are some of the group of drugs that have been tried in COVID treatment.

Protease inhibitors[2]

The host cell protease activates the envelop glycoprotein and thus enters the viral cell. Protease inhibitors such as Lopinavir, Ritonavir, Darunavir, Danoprevir and the experimental drug ASC-09 have known to be exceptional targets for patients having COVID-19 symptoms. Among these agents, the most common protease inhibitor was Lopinavir/Ritonavir combination, using a dosing regimen of 400 mg/100 mg Lopinavir/Ritonavir twice daily for up to 14 days which was reported in 18 published studies. Certain studies have shown to be of some benefit when patients were given the drug therapy earlier (within 12 days of symptom onset) as they experienced a shorter time to clinical improvement (HR 1.25; 1.77–2.05 versus 1.30; 0.84–1.99). The studies from real-world evidence of Darunavir and Danoprevir have been reported from two countries, that is, Germany and China. Haerter et al (2020) in Germany reported the outcomes of a case series of 33 patients with COVID who were previously treated for HIV and were on antiretroviral treatment including Darunavir. The outcomes were such that three patients recovered from COVID and one died in this course of treatment[3]. Shi et al. (2020) in China reported in their case series on the limited efficacy of darunavir in terms of reducing duration from illness onset to admission and clinical symptoms. Zhang et al (2020), on analyzing 33 COVID patients (10 mild cases, 22 moderate cases, and one severe case) concluded that Danoprevir produced superior efficacy to Lopinavir-Ritonavir combination[4].

Broad-spectrum Antivirals

Umifenovir is a broad-spectrum antiviral licensed in China and Russia for influenza and it inhibits the fusion of the viral envelope with host cell cytoplasmic membrane[5]. Few effects in decreasing the risk of COVID-19 transmission were seen with the drug. It was advised for post-exposure prophylaxis in a dose of 200 mg orally every 8 h[5]. In an early pilot study from China, treatment with Umifenovir was found to reduce SARS-CoV-2 viral loads, with 94% of patients treated with Umifenovir reported negative SARS-CoV-2 viral load compared to 53% in the control[6]. Nevertheless, the results from two RCTs suggested limited efficacy in treating COVID-19, as the recovery rates were comparable with control[7,8].

RNA-dependent RNA Polymerase (RdRP) Inhibitor

- *Favipiravir*

Favipiravir is an oral pyrazine carboxamide derivative and guanine analog which selectively inhibits the RNA-dependent RNA polymerase (RdRP) of RNA viruses [9]. RdRP is required during the replication process of RNA viruses as it determines the replication rates and mutation of the virus to adapt to the new host environment, which ultimately influences its fidelity. The RdRP targeting has become another mainstay in the treatment of SARS-CoV-2. A pilot study was

conducted in China by Cai et al on 80 patients with COVID-19 who were treated with Favipiravir with a loading dose of 1600 mg followed by a maintenance dose of 600 mg three times daily for up to 14 days. After 14 days of treatment, it was concluded that patients treated with Favipiravir had better treatment outcomes in terms of disease progression and viral clearance compared to those treated with lopinavir/ritonavir[10]. Randomized control trials on Favipiravir had reported higher 7-day recovery rates and symptom improvements such as pyrexia and cough[11,12]. With no significant adverse events were reported, favipiravir is currently being used in the treatment of mild to moderate cases of SARS-CoV-2 infection.

- *Remdesivir*

Remdesivir is another nucleotide analog inhibitor of RdRP that have been extensively examined as a potential anti SARS-CoV-2 medication. One of the first case papers in the United States on the use of Remdesivir was published by Holshue et al. (2020), which reported improvement in the patient's condition after treatment[13]. Proceeding, two RCTs on Remdesivir have been conducted using a dose of Remdesivir 200 mg on day 1, followed by 100 mg daily for up to 10 days. In the first RCT of 237 patients with COVID-19, the authors found that patients on Remdesivir had clinical improvements after 28 days, and they reported faster time to symptom improvement compared to control[14]. A large multicentric randomized clinical trial reported by Beigel et al. (2020) with 1107 patients from Europe, Asia, and America treated with either Remdesivir or placebo for 10 days found that the median time to recovery was much faster with Remdesivir treatment, with a significantly higher number of patient who recovered; but, it does not address the adverse effects and more clinical trials are underway to examine the potential of this drug in SARS-CoV-2[15].

Nucleoside and Neuraminidase Inhibitors

- *Oseltamivir*

Neuraminidase inhibitors such as Oseltamivir are another class of drugs that were used for the treatment of SARS-CoV-2. As the viral outbreak of SARS-Cov-2 in China occurred during the peak influenza season, a huge patient population had received Oseltamivir therapy[14,16]. Several randomized clinical trials are currently under evaluation for the effectiveness of Oseltamivir either alone or as a combination with Chloroquine and Favipiravir. Chiba et al in his study stated that early Oseltamivir administration may lower the duration of fever in COVID-19-suspected outpatients without hypoxia when it is used in combination with antibacterial therapy[17]. However, due to its mechanism of action, there is a limited role of this drug in the management of COVID-19 after the exclusion of influenza.

- *Ribavirin and Azuvudine*

Neuroamidase inhibitors ribavirin and Azvudine have been recommended in the initial stages for patients with SARS-CoV2 infection, given that the symptoms were thought to be due to pneumonia.

There is currently no evidence to suggest that Ribavirin when used alone offers any benefit in the management of COVID-19. Hung et al (2020) in a phase 2 trial, showed the effect of the combination therapy of Ribavirin, Lopinavir/Ritonavir and interferon beta-1b to have some beneficial results, and more studies are needed to further confirm and conclude. However, as Ribavirin causes dose-dependent hematological toxicity, and is a known teratogen there is the limited value of this drug in the treatment of COVID-19[18].

Polymerase Acidic Endonuclease Inhibitor

The only drug in this class examined was BaloxavirMarboxil. This drug targets the viral polymerase acidic protein to block the endonuclease function, resulting in the inhibition of virus mRNA transcription and infection[19, 20]. In an exploratory RCT by Lou et al (2020), COVID-19 confirmed cases were randomized (1:1:1) to either receive Favipiravir for 14 days or BaloxavirMarboxil (80 mg once a day orally on Day 1 and Day 4) or control group. They concluded that adding either Baloxavir or Favipiravir under the trial dosages to the existing standard treatment was beneficial in COVID-19 patients[21].

II. Corticosteroids

High-dose glucocorticoid (GC) therapy was suggested in the treatment of severe Covid cases with pneumonia and also with moderate to severe respiratory insufficiency[22]. Some animal studies have contributed to generate evidence for the use of glucocorticoids during the acute phase of severe disease to (i) reduce inflammation, (ii) attenuate acute lung injury, and (iii) improve survival[23]. A recent meta-analysis by Medhuri et al has evaluated prolonged Methylprednisolone therapy for ARDS and concluded a significant reduction in mortality, with an increase in ventilator-free days (13 vs. 7, $p < 0.001$) by lowering the circulatory levels of proinflammatory mediators[23].

Huang et al, in their study, suggested that a subset of patients with severe COVID-19 may have cytokine storm syndrome[24], which is a condition frequently related to lung involvement and multi-organ failure. Therefore, systemic GC administration is empirically indicated for severe complications in order to suppress cytokine storm syndrome manifestations like ARDS, acute heart injuries, acute kidney complications, and higher D-dimer levels[24]. This was also supported by Villar et al. who showed that the use of dexamethasone was associated with better survival in ARDS[25].

However, GC has no role in mild disease. A study by Ling Y et al in Covid convalescent patients reported that there was no difference in 90-days mortality with GC therapy, and these patients were associated with delayed viral clearance and hence it was not recommended in mild disease [26]. Veronese et al also reported that the duration of viral RNA in oropharyngeal swabs and feces doubled in the corticosteroids group compared to controls[27].

Ideally, glucocorticoids should be used in a lower dose and for a short duration (methylprednisolone, <1 mg/kg body weight, no more than 7 days), along with adverse drug reaction monitoring. In addition, a long-term follow-up (6 months to 3 years) is essential to identify delayed adverse effects in these patients[28]. Excessive cumulative dose or dose > 240mg hydrocortisone-equivalent, causes side effects, including hyperglycemia, psychosis, secondary infection, and vascular necrosis[28]. Moreover, adequate and prolonged glucocorticoid supplementation has proved to mitigate the Critical Illness Related Corticosteroid Insufficiency (CIRCI), thus enhancing the resolution of lung and systemic inflammation [29].

III. Interferons

Interferon-alpha & beta treatment is found to significantly reduce the duration of detectable virus in the upper respiratory tract and reduced the duration of elevated blood levels for the inflammatory markers, IL-6, and CRP in confirmed COVID cases[30]. The dose given was 5 mU twice a day by nebulizer for 10 days[30].

IFN-beta increases CD73 in pulmonary capillaries, which is responsible for providing vascular integrity under hypoxic conditions. Hence, the administration of intravenous IFN-beta is recommended in severe COVID cases with ARDS. It is also advised in critically ill patients with compromised peripheral circulation[31].

IV. Immunomodulators

In the latter phase of convalescence, hospitalized patients with COVID-19 can develop a syndrome of dysregulated and systemic immune overactivation described as a cytokine storm or hyperinflammatory syndrome that worsens acute respiratory distress syndrome and can lead to multisystem organ failure. Therapeutic agents targeting the immune interaction between SARS-CoV-2 with the inflammatory system[32].

Anti-Interleukin Receptor Monoclonal Antibody

- *Tocilizumab*

It has been recommended in patients with moderate disease with progressively increasing oxygen requirements and mechanically ventilated patients not improving despite the use of steroids and in patients having elevated level of inflammatory markers (e.g., CRP, Ferritin, IL-6) by Clinical Management Protocol: Covid-19 (version 3), Ministry of Health and Family Welfare, India[33]. A retrospective analysis of 20 severe cases of COVID-10 showed that treatment with Tocilizumab led to a reduction in fever and lung lesion opacity, and recovered the percentage of lymphocytes in peripheral blood[34]. It is given in the dose of 8mg/kg (maximum 800 mg at a time) slowly in 100 ml NS over 1 hour OD/BD[33].

- *Sarilumab*

Another interleukin-6 inhibitor, Sarilumab is under evaluation. The efficacy and safety of Sarilumab 400 mg IV and sarilumab 200 mg IV versus placebo was evaluated in patients hospitalized with COVID-19 in an adaptive Phase 2 and 3, randomized (2:2:1), double-blind, placebo-controlled trial and noted a reduction in levels of CRP in critically ill patients[35].

Anti-Interleukin-6 Antibody

- *Siltuximab*

Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors, inhibiting IL-6 signaling [36]. Siltuximab is dosed as an IV infusion. In a study by Gritti et al (n=21), siltuximab administered intravenously at a dose of 11 mg/kg/day over 1 hour, and the decision of the administration of second dose of Situximab was given 2-3 days apart based on physician's acumen[37]. They found that serum CRP and inflammatory markers were within normal range between the 5th-7th day of treatment, in patients requiring ventilatory support; clinical recovery also correlated[37].

- *Itolizumab*

Itolizumab is a first class humanized IgG1 monoclonal antibody developed by Biocon and the Center of Molecular Immunology, Havana. It is DCGI approved based on positive data from a RCT conducted in several hospitals of Mumbai and Delhi. The mechanism of Itolizumab is it selectively targets the CD6, a T-cell marker involved in stimulation, maturation, and adhesion of T cells. Its likely mechanism in COVID is binding to CD6 causing downregulation of T lymphocyte cells activation, causing a reduction in synthesis of pro-inflammatory cytokines thus reducing the role of T cell infiltration at the site of inflammation.It is mainly used for the treatment of chronic plaque psoriasis. In COVID 19 crisis this drug came to use for its suppression of pro-inflammatory properties and is said to be the first new biological therapy approved globally for COVID 19 complications. Dosage approved is 25 mg/5ml injection solution to treat cytokines release syndrome (CRS) aka 'Cytokine storm' and in moderate to severe acute respiratory distress syndrome patients of COVID 19.

V. Anti-Microbial Agents

Chen et al.[38] reported that 15% of COVID-19 patients received antifungal treatment and 71% received antibiotic treatment, 25% of whom were treated with a single antibiotic, and 45% with combination therapy. The antibiotics used were Cephalosporins, Quinolones, Carbapenems, Tigecycline, and Linezolid. Wang et al. explained that many sick patients received antibacterial therapy, such as

Moxifloxacin (64%), Ceftriaxone (25%), and Azithromycin (18%)[39]. Other antibiotics proposed for the treatment of COVID-19 disease are Azithromycin, Quercetin, Rapamycin and Doxycycline [40,41]. However, the combination of hydroxychloroquine and azithromycin appeared to be even more effective in COVID-19 treatment. Azithromycin also inhibits the replication of other viruses, such as Zika and Ebola. Azithromycin, Doxycycline, and Rapamycin are antibiotic drugs that inhibit protein synthesis and functionally reduce inflammation and viral replication. So, inhibiting virus production should help to clinically reduce virus transmission to other patients[41]. The current ministry of health guidelines has mentioned the use of the Ivermectin-Doxycycline combination for mild to moderate COVID-19 cases[33]. The adult dose of Ivermectin is 12mg daily for 3 days and that of Doxycycline is 100mg BD for 5 days[33].

VI. Anticoagulants

While mortality in COVID-19 can be largely attributed to hypoxemia secondary to acute respiratory distress syndrome (ARDS), there is growing suspicion that thromboembolic events could also be contributing to the overall picture, as described in the article published by Cui S et al[42]. While the pathophysiology behind the hypercoagulable state in COVID-19 is still under investigation, several proposed mechanisms have been described. Disseminated intravascular coagulation (DIC), properties of the virus itself, antiphospholipid syndrome, activation of the complement cascade, and endothelial dysfunction induced by the infection have been described in the possibilities[43,44].

Anticoagulation therapy recommendation for COVID-19 patients are[45]:

- The suggested anticoagulation therapy according to the clinical severity of COVID-19, adjusted based on the thrombotic and bleeding risk of the patients is as follows.
- No anticoagulation: The following patients do not need anticoagulation. Ambulant COVID-19 patients with or without constitutional/respiratory symptoms. Patients with mild or moderate COVID and high bleeding risk abnormal aPTT or PT need not be a contraindication for anticoagulation, when necessary. Clinical judgment is advocated and treatment may be individualized based on the risk and benefit.
- Prophylactic anticoagulation dose: The following patients can be given prophylactic anticoagulation dose- Hospitalized mild COVID-19, with evidence of lung involvement, without high bleeding risk. Patients hospitalized with moderate COVID-19 with low VTE risk and low bleeding risk. Patients with severe COVID-19 with high bleeding risk and low VTE risk / low ISTH- DIC score.
- Intermediate anticoagulation dose: Following patients can be given intermediate anticoagulation dose- Hospitalized severe COVID -19 patients with low VTE / low ISTH-DIC score and low bleeding risk.

- Therapeutic anticoagulation dose: Following patients can be given therapeutic anticoagulation dose-
- Patients with documented thrombotic events like DVT, acute pulmonary embolism, device thrombosis, etc. Patients with high suspicion of thrombotic events, when imaging is not possible.
- Patients with pre-existing clinical indications for therapeutic anticoagulation like atrial fibrillation (AF), Prosthetic valves, etc.
- Patients receiving renal replacement therapy (RRT)or those on Extracorporeal membrane oxygenation (ECMO).
- Patients with severe COVID-19 with low bleeding risk and high-risk features/ high ISTH-DIC score

Thrombolytic therapy for Pulmonary embolism

Hemodynamically unstable patients should receive reperfusion therapy. Considering the high likelihood of bleed in COVID-19, it has been recommended to use half dose thrombolytic therapy and watch for the response, and complete the full course only if the response to half dose is not good.[37]

Mechanical thromboprophylaxis: In patients with definite indications for anticoagulant therapy, but with contraindications for anticoagulation, methods of mechanical thromboprophylaxis like pneumatic compression are encouraged.

Conclusion

A large number of studies are being conducted every day since the beginning of the pandemic to determine the beneficial role of various groups of drugs to combat the COVID 19 disease. As more and more drugs are explored, the capability of the healthcare system to handle the situation has improved which is evident from the decrease in the case mortality rate. Further discoveries and the arrival of vaccination will only add to our understanding of this viral disease and may enable us to check and control the disease.

References

1. *Coronavirus Update (Live): 10,819,762 Cases and 519,272 Deaths from COVID-19 Virus Pandemic - Worldometer [Internet]. Worldometers.info. 2020 [cited 10 Jan 2020]. Available from: https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1?*

2. *Teoh SL, Lim YH, Lai NM, Lee SW. Directly Acting Antivirals for COVID-19: Where Do We Stand? Frontiers in microbiology. 2020;11:1857.*

3. *Haerter G, Spinner CD, Roider J, Bickel M, Krznaric I, Grunwald S, et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. Infection. 2020:1.*

4. *Zhang Z, Wang S, Tu X, Peng X, Huang Y, Wang L, et al. A comparative study on the time to achieve negative nucleic acid testing and hospital stays between danoprevir and lopinavir/ritonavir in the treatment of patients with COVID-19. J Med Virol. 2020 Nov;92(11):2631-2636.*

5. *Liu W, Zhou P, Chen K, Ye Z, Liu F, Li X, et al. Efficacy and safety of antiviral treatment for COVID-19 from evidence in studies of SARS-CoV-2 and other acute viral infections: a systematic review and meta-analysis. CMAJ. 2020 Jul 6;192(27):E734-E744.*

6. *Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, Hong Z, Xia J. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J Infect. 2020 Jul;81(1):e1-e5.*

7. *Chen W, Yao M, Fang Z, Lv X, Deng M, Wu Z. A study on clinical effect of Arbidol combined with adjuvant therapy on COVID-19. J Med Virol. 2020 Nov;92(11):2702-2708.*

8. *Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial. Med (N Y). 2020 Dec 18;1(1):105-113.e4.*

9. *Agrawal U, Raju R, Udwadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19. Med J Armed Forces India. 2020 Oct;76(4):370-376.*

10. *Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020 Oct;6(10):1192-1198.*

11. *Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv [Preprint] doi: https://doi.org/10.1101/2020.03.17.20037432 [Internet]. [cited 25 October 2020]. Available from: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v4.*

12. *Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical Outcomes and Plasma Concentrations of BaloxavirMarboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. Eur J Pharm Sci. 2021 Feb 1;157:105631*

13. *Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020 Mar 5;382(10):929-936.*

14. *Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe*

COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020 May 16;395(10236):1569-1578. doi: 10.1016/S0140-6736(20)31022-9.

15. *Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Nov 5;383(19):1813-1826.*
16. *Malosh RE, Martin ET, Heikkinen T, Brooks WA, Whitley RJ, Monto AS. Efficacy and safety of oseltamivir in children: systematic review and individual patient data meta-analysis of randomized controlled trials. Clinical Infectious Diseases. 2018 May 2;66(10):1492-500.*
17. *Chiba S. Effect of early oseltamivir on outpatients without hypoxia with suspected COVID. Wien KlinWochenschr. 2020 Dec 9:1–6.*
18. *Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet. 2020 May 30;395(10238):1695-704.*
19. *Koszalka P, Tilmanis D, Roe M, Vijaykrishna D, Hurt AC. Baloxavirmarboxil susceptibility of influenza viruses from the Asia-Pacific, 2012–2018. Antiviral Research. 2019 Apr 1;164:91-6.*
20. *Locke SC, Splawn LM, Cho JC. Baloxavirmarboxil: a novel cap-dependent endonuclease (CEN) inhibitor for the treatment of acute uncomplicated influenza. Drugs of today (Barcelona, Spain: 1998). 2019 Jun;55(6):359-66.*
21. *Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical Outcomes and Plasma Concentrations of BaloxavirMarboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. Eur J Pharm Sci. 2021 Feb 1;157:105631*
22. *Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020 Feb 29;395(10225):683-684.*
23. *Meduri GU, Siemieniuk RAC, Ness RA, Seyler SJ. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. J Intensive Care. 2018 Aug 24;6:53.*
24. *Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.*
25. *Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020 Mar;8(3):267-276.*
26. *Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl). 2020 May 5;133(9):1039-1043.*

27. *Veronese N, Demurtas J, Yang L, Tonelli R, Barbagallo M, Lopalco P, et al. Use of Corticosteroids in Coronavirus Disease 2019 Pneumonia: A Systematic Review of the Literature. Front Med (Lausanne). 2020 Apr 24;7:170.*

28. *Zhou W, Liu Y, Tian D, Wang C, Wang S, Cheng J, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. Signal transduction and targeted therapy. 2020 Feb 21;5(1):1-3.*

29. *Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Intensive Care Med. 2017 Dec;43(12):1781-1792.*

30. *Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, et al. Interferon-á2b Treatment for COVID-19. Frontiers in Immunology. 2020 May 15;11:1061.*

31. *Jalkanen J, Hollmén M, Jalkanen S. Interferon beta-1a for COVID-19: critical importance of the administration route. Critical Care. 2020 Dec;24(1):1-3.*

32. *Ingraham NE, Lotfi-Emran S, Thielen BK, Techar K, Morris RS, Holtan SG, Dudley RA, Tignanelli CJ. Immunomodulation in COVID-19. Lancet Respir Med. 2020 Jun;8(6):544-546.*

33. *Clinical management protocol: COVID-19 version 3 [Internet]. Mohfw.gov.in. 2020 [cited 3July 2020]. Available from: https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19.pdf*

34. *Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences. 2020 May 19;117(20):10970-5.*

35. *Sanofi S. Regeneron provide update on Kevzara®(sarilumab) Phase 3 US trial in COVID-19 patients. 2020.[Internet]. [Cited on October 25, 2020]. Available at: https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00.*

36. *Interleukin-6 Inhibitors: COVID-19 Treatment Guidelines. 2020 [Internet]. [cited 25 October 2020]. Available from: https://www.covid19treatmentguidelines.nih.gov/immune-based- herapy/immunomodulators/interleukin-6-inhibitors/*

37. *Gritti G, Raimondi F, Ripamonti D, et al. IL-6 signalling pathway inactivation with siltuximab in patients with COVID-19 respiratory failure: an observational cohort study. medRxiv [Preprint] 2020. dOI: 10.1101/2020.04.01.20048561. [Internet]. [cited 25 October 2020]. Available from:https://www.immunology.ox.ac.uk/covid-19/covid-19-immunology-literature-reviews/use-of-siltuximab-in-patients-with-covid-19-pneumonia-requiring-ventilatory-support.*

38. *Chen N, Zhou M, Dong X et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–13.*

39. *Wang D, Hu B, Hu C et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061–9.*

40. *KamaliAghdam M, Jafari N, Eftekhari K. Novel coronavirus in a 15-dayold neonate with clinical signs of sepsis, a case report. Infect Dis (Lond) 2020;52: 427–9.*

41. *Miranda C, Silva V, Capita R, Alonso-Calleja C, Igrejas G, Poeta P. Implications of antibiotics use during the COVID-19 pandemic: present and future. J AntimicrobChemother. 2020 Dec 1;75(12):3413-3416.*

42. *Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. [Published online ahead of print April 9 20202]. J ThrombHaemost. April 2020. 10.1111/jth.14830.*

43. *Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect. 2020 Dec;9(1):687-690.*

44. *Campbell CM, Kahwash R. Will Complement Inhibition Be the New Target in Treating COVID-19-Related Systemic Thrombosis? Circulation. 2020 Jun 2;141(22):1739-1741.*

45. *Gnanaraj JP, Princy A, Majella CM, Durairaj P, Edwin R, Kannan K et al. Antithrombotic Therapy in COVID-19 -A Scientific Position Statement by Heart Disease Management Program, National Health Mission, Government of Tamil Nadu. The Journal of the Association of Physicians of India; 2021:69:82-87.*

Dr. ShwetaSurve*, Dr. NehaSawant* *Speciality Medical Officer, Department of Pharmacology

GLOBAL RACE OF VACCINES TARGETING SARS-COV-2 DURING THE ONGOING COVID-19 PANDEMIC

Dr. ShwetaSurve*, Dr. NehaSawant*

**Speciality Medical Officer, Department of Pharmacology*

Abstract

There is an unprecedented need to manufacture and distribute enough safe and effective vaccines to immunize an extraordinarily large number of individuals to protect the entire global community from the continued threat of morbidity and mortality from severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2). The global need for a vaccine and the wide geographic diversity of the pandemic requires more than one effective vaccine approach. The current COVID-19 vaccine pipeline comprises a broad range of technology platforms, including both traditional and novel approaches. Early data are emerging for the most advanced clinical candidates, and although encouraging antibody and T cell responses have been reported for vaccines based on several of the different platforms being used, it is too early to assess their relative potential.

Keywords: *mRNA-based vaccines, viral vector vaccines, S protein.*

Background of COVID 19

The coronavirus disease 2019 (COVID-19) pandemic caused by a novel coronavirus, SARS-CoV-2, has infected more than 4.9 million individuals and resulted in over 300,000 deaths globally. The rapid spread of the virus and the precipitously increasing numbers of cases necessitate the urgent development of accurate diagnostic methods, effective treatments, and vaccines [1].

Two countermeasures with promise for controlling the current SARS-CoV-2 pandemic are recombinant neutralizing antibodies and vaccines directed against the virus that causes COVID-19. Although other measures designed to respond to and control a pandemic such as surveillance, quarantine, and social distancing work efficiently to flatten the curve at a major cost to the economy, the development and deployment of effective tests, drugs, and vaccines to protect lives and limit disease spread are still urgent [2]. Emergency Use Authorizations (EUA) expedite the availability of drugs to prevent serious or life-threatening diseases or conditions when there are no adequate, approved, and available alternatives. For many drugs that are already marketed for other conditions, off-label use can increase access for patients who need them [3]. Vaccine development is the most effective strategy to prevent and eliminate the infectious disease. By learning from the vaccine

Dr. ShwetaSurve*, Dr. NehaSawant* *Speciality Medical Officer, Department of Pharmacology

development path of MERS and SARS, several platforms are being investigated. Since the genetic sequence of SARS-CoV-2 has been released on 11 January 2020, more than 40 pharmaceutical companies and academic institutions from many countries have engaged in actively developing COVID-19 vaccines, and some candidates have entered efficacy evaluation in animals and clinical trials.

Challenges for vaccine development

The quest for a vaccine against the novel SARS-CoV-2 is recognized as an urgent issue. Effective vaccination could indeed play a significant role in curbing the spread of the virus and help to eliminate it from the human population. However, scientific efforts to address this challenge are only just beginning. Much remains to be learned about the virus, its biological properties, epidemiology, etc. At this early stage, there is also a lack of information about specific immune responses against SARS-CoV-2, which presents a challenge for vaccine development [4].

Reasons for the lack of commercial and effective vaccines for SARS and MERS are varied. In the case of MERS, the vaccine development was likely delayed because of the scarcity of suitable and cost-effective small animal models during pre-clinical experimentation. Besides, probably, a vaccine has not been delivered because of the low interest in investing in a vaccine for a disease that has produced relatively low and geographically centralized cases (compared with other more global and persistent infectious diseases such as influenza, HIV, and tuberculosis). This last factor might have also contributed to the lack of a vaccine for SARS, in the sense that it was considered pointless to continue investing in a vaccine for a disease whose cases ceased to be reported in 2004.

Although no vaccines are commercially available for SARS and MERS, past and current vaccine development efforts against these diseases might be of high value for the development of an effective vaccine for COVID-19. The present review aims to describe the possible implications of creating an effective vaccine against COVID-19 taking as a starting point results obtained from other clinically relevant coronavirus strains. We focused our review on active immunization approaches as this offers the possibility of long-term prevention for these diseases.

Vaccine development

Unlike typical vaccine development, which often takes decades, developing a vaccine to prevent COVID-19 has become a race between humans and the virus. Many countries have accelerated the process of clinical trials to determine an effective and safe vaccine to prevent COVID-19 and influence the course of the current pandemic[5]. Currently, about 250 candidate vaccines against SARS-CoV-2 are in development worldwide, including mRNA vaccines, replicating or non-replicating viral vectored vaccines, DNA vaccines, autologous dendritic cell-based vaccine, and inactive virus vaccines.[6]

Dr. ShwetaSurve*, Dr. NehaSawant* *Speciality Medical Officer, Department of Pharmacology

Mechanism of action of various vaccine candidates [7]

The most effective licensed vaccines elicit long-term antigen-specific antibody responses by plasma cells in addition to the development of persisting T cell and B cell memory. In the case of SARS-CoV-2 infection, both humoral and cellular immune responses are crucial for the clearance of infection.

- Recombinant virus vectors work similarly to an endogenous pathogen, by expressing axenic target protein in the cytoplasm of the host cell. After processing of such endogenous antigen, MHC class 1 molecules present them to CD8+ T lymphocytes, which causes the production of T-cytotoxic cells. This pathway leads to the establishment of cell-mediated immunity, which is crucial in getting rid of virus-infected cells.

- Subunit vaccine candidate particularly receptor-binding domain (RBD) of S protein of SARS-CoV-2 contains major antigenic determinants that can induce neutralizing antibodies. The SARS-CoV-2 S protein can also induce CD8+ T-cell responses. The RBD of S protein contains multiple conformation-dependent epitopes and is the main domain that induces neutralizing antibody and T-cell immune responses against SARS-CoV-2 infection making it an important target for vaccine development.

- Adenoviral vectors can induce potent antibody as well as T cell responses with variations in the immune response depending on the serotype employed. Replication-deficient Ad5, one of the most widely used adenoviral vectors, can induce exceptionally potent CD8+ T cell as well as antibody responses.

- Furthermore, DNA vaccination is also able to elicit both humoral and cellular immune responses, through activation of CD8+ cytotoxic and CD4+ helper T cells, respectively. Upon entry in the cell, DNA vaccines are sensed by a variety of innate immune receptors i.e. STING/TBK1/IRF3 pathways and the AIM2 inflammation and many other factors are involved in DNA vaccine mode of action

- Another nucleotide-based vaccine i.e. Exogenous mRNA is also immunostimulatory, as it is recognized by a variety of cell surface, endosomal and cytosolic innate immune receptors. Mammalian cells can sense foreign RNA via Pattern recognition receptors (PRRs) such as TLR3, TLR7, and TLR8 located in the endosomes and RIG-I, MDA-5, and PKR located in the cytoplasm as well as NLRP3 and NOD. Activation of the PRRs by mRNA vaccines results in a robust innate immune response including the production of chemokines and cytokines such as IL-12 and TNF at the inoculation site, which are innate factors crucial for the induction of an effective adaptive immune response against the encoded antigen. ID immunization with mRNA vaccines upregulates the expression of chemokines including the CXCR3-ligands CXCL9, CXCL10, and CXCL11, that recruit innate immune cells such as DCs and

Dr. ShwetaSurve*, Dr. NehaSawant* *Speciality Medical Officer, Department of Pharmacology

macrophages, to the site of injection. The mRNA vaccines can also induce an immunological repertoire associated with the generation of high magnitude long-lived antibodies

Diversity of technology platforms [8, 9]

A striking feature of the vaccine development landscape for COVID-19 is the range of technology platforms being evaluated which includes

1) Nucleic acid vaccines (RNA & DNA)
2) Protein-based vaccines (Subunit & virus-like particles)
3) Virus vaccines (live attenuated & inactivated)
4) Viral vector (replicating & non replicating)

Prime targets for the development of the SARS & MERS vaccine were S protein & its fragments such as S1, S2, RBD, and N protein hence, it is expected that similar regions of SARS-CoV-2 could be considered as targets for COVID-19 vaccines.

1) Nucleic acid vaccines

a) **mRNA-based vaccines** – Comprise of mRNA that encodes a protein antigen. Conventional mRNA-based vaccines encode the antigen of interest and contain 50 and 30 untranslated regions, whereas the virally derived, self-amplifying RNAs encode not only the antigen but also the viral replication machinery that enables intracellular RNA amplification and abundant protein expression. Recent mRNA vaccine designs have improved the stability and proteintranslation efficiency for enhancedinnate and adaptive immunogenicity. Delivery of themRNA vaccine has been optimized by the use of lipid nanoparticles for intramuscular or intradermal administration. Additionally, unlike conventional vaccines, which are madefrom either inactivated pathogens or the small subunit of live pathogens, no infectious virus needs to be handled for mRNA vaccines. Therefore, testing is relatively safe, efficient, cost-effective, and rapid. Both Moderna/NIH and CureVac are focusing on mRNA vaccine development, and a safety clinical trial of Moderna's candidate vaccine mRNA-1273 with a size of 45 volunteers was performed in March 2020.

b) DNA vaccines

DNA vaccines, another type of nucleic acid-based vaccine, consist of plasmid-DNA encoding one or several antigens that will be expressed in host cells. DNA vaccines can be produced rapidly and at a low cost. However, the need for specific delivery systems to achieve good immunogenicity and possible genomic integration and persistence in host cells is a remaining concern. DNA vaccines encoding the S protein of the SARS-CoV and MERS-CoV have been shown to elicit T cell and neutralizing antibody responses,

Dr. ShwetaSurve*, Dr. NehaSawant* *Speciality Medical Officer, Department of Pharmacology

as well as protective immunity in a mouse model and human studies. INO-4800 is a DNA vaccine candidate targeting the S protein of SARS-CoV-2.

2) Subunit vaccines

Subunit vaccines based on recombinant S or S1 protein of SARS CoV and MERS-CoV have been demonstrated to be efficacious in many studies. Clover Biopharmaceuticals is developing a vaccine consisting of a trimerized SARS-CoV-2 S protein using their patented Trimer-Tag technology. The receptor-binding domain (RBD) in SARS-CoV-2 S protein was identified, and it was further demonstrated that SARS-CoV-2 RBD exhibited significantly higher binding affinity to ACE2 receptor compared to binding between SARS-CoV RBD and ACE2, suggesting that the RBD-based SARS CoV vaccines have the potential to be developed for the prevention of SARS-CoV-2 infections. The pulmonary surfactant-biomimetic nanoparticles used to potentiate heterosubtypic influenza immunity can be used as an adjuvant to enhance the immunogenicity of SARS-CoV-2 subunit vaccines.

3) Inactivated or live-attenuated virus vaccines

The traditional vaccine strategy included whole inactivated or live-attenuated virus vaccines. Researchers at the University of Hong Kong have developed a live influenza vaccine that expresses SARS CoV-2 proteins. Codagenix has developed a “codon deoptimization” technology to attenuate viruses, and the company is exploring COVID-19 vaccine strategies. Generation of an inactivated whole-virus (IWV) vaccine is the quickest approach for vaccine production following a new outbreak. Such vaccines have successfully been developed for influenza virus and enterovirus 71. IWV vaccines are usually made by exposure of a virulent virus to chemical or physical agents, e.g., formaldehyde or gamma irradiation, to destroy infectivity while retaining immunogenicity. The need to use large amounts of antigen to elicit an adequate antibody response and the possibility of causing Th2-bias hypersensitivity are major concerns for IWV vaccines. One inactivated vaccine candidate that displayed good cross-neutralization to different COVID-19 strains has received approval for testing in human trials.

4) Virus vector-based vaccines

Viral vector vaccines are also potential tools for vaccine development. These vaccines can specifically deliver genes to target cells, enhance immunogenicity without an adjuvant, and induce a robust cytotoxic T cell response to eliminate virus-infected cells. Although the results of viral vector-based vaccines have been encouraging in animal models, some obstacles need to be overcome before use in humans. These obstacles include genetic stability, the ability to evade preexisting immunity, and genotoxicity. Adenovirus serotype 5 (Ad5) is the most widely used vector because this vector can be easily produced and has

Dr. ShwetaSurve*, Dr. NehaSawant* *Speciality Medical Officer, Department of Pharmacology

high levels of transgene expression and a broad range of viral tropism.The ability to enhance mucosal immunity through targeting epithelial cells of the upper respiratory tract and gut, two main sites that express high levels of the ACE2 receptor for SARS-CoV-2, makes Ad5 an advantageous viral vector against COVID-19. Recombinant Ad5 vector-based vaccines have been examined in clinical trials against infectious diseases. Johnson & Johnson is developing an adenovirus vectored vaccine using AdVac®/PER.C6® vaccine platforms.

The first COVID-19 vaccine candidate based on adenovirus vectored vaccine developed by Chen Wei group entered human clinical testing (NCT04313127) with unprecedented rapidity early on 16 March 2020. The candidate vaccine Ad5-nCoV, which encodes a full-length S protein of SARS-CoV-2, proceeded to a Phase II clinical trial in China. Another viral vector vaccine, ChAdOx1 nCoV-19 (also known as CoviShield), is composed of a nonreplicating chimpanzee adenovirus vector and a genetic sequence of S protein. The vector represents an attractive alternative to the human adenoviral vector due to its good safety profile and lack of preexisting immunity in the human population. Apart from the adenovirus vector-based vaccine, two lentivirus vector-based vaccine candidates have been developed. Lentivirus vector (LV) systems represent an attractive technology for vaccine development. In addition to their ability to effectively deliver genes or antigens of interest into cells and to generate a humoral and cellular mediated immune response against the encoded transgenes, LVs can transduce antigen-presenting cells (APCs), the main cell types mediating the immune response, at high efficiencies with little to no cytotoxicity. Through up or downregulation of immune-modulatory genes in APCs by LVs, the genetically modified APCs may potentially activate a strong protective immunity against infections. Two vaccine candidates, Covid-19/ APC vaccine and LV-SMENP-DC vaccine, which were made by modifying artificial APCs and dendritic cells with LVs expressing multiple viral genes and immune-modulatory genes, act as 'Trojan horses' against the SARS-CoV-2 virus. Clinical trials are currently underway to evaluate their safety and immune reactivity.

Probiotics: Bifidobacterium is one of the domestic, nonpathogenic anaerobic bacteria found in the intestine of humans. These organisms are believed to have health-promoting properties for their host, including increasing the immune response and protecting the host against viral infection. As vaccine vectors, they offer several advantages including low cost, low resistance to antibiotics, noninvasive administration, and high safety levels. The most attractive feature is that Bifidobacterium tends to elicit high levels of mucosal antibodies against the expressed foreign antigen following uptake via the mucosal immune system. Some strains of Bifidobacterium have been used as a delivery vector for the development of vaccines against Hepatitis C virus and enterovirus 71. The bacTRL-Spike vaccine candidate contains live Bifidobacteriumlongum, which contains synthetic plasmid DNA encoding the S protein of SARS-CoV-2. The ongoing trial is designed to evaluate the safety and tolerability of the orally delivered bacTRLSpike vaccine in healthy adults.

Dr. ShwetaSurve*, Dr. NehaSawant* *Speciality Medical Officer, Department of Pharmacology

Table 1: List of vaccine candidates for COVID-19 under evaluation[10]

Vaccine Platform	Name of the vaccine candidate	Dosing with the route of administration	Phase of Trial
DNA plasmid vaccine	INO-4800	0,28 days (ID)	Phase 2a (NCT04447781)
	BacTRL-Spike (DNA plasmid expressing trimeric S within B. longum)	Oral capsule	Phase 1 (NCT04334980)
Lipid nanoparticle encapsulated mRNA	mRNA-1273	0, 28 days (IM)	Phase 2 (NCT04470427)
	BNT162 (a1,b1,b2,c2)	0, 28 days (IM)	Phase 3 (NCT04368728)
Protein subunit	Adjuvant recombinant protein (RBD-Dimer)	0,28 or 0,28,56 days (IM)	Phase 2 (NCT04466085)
Adenovirus Type5 (Non-replicating viral vector)	Ad5-nCoV	1 dose (IM)	Phase 2 (ChiCTR2000031781)
Adenovirus vector	ChAdOx1 nCoV-19	1 dose (IM)	Phase 3 (ISRCTN89951424)
Lentivirus vector	Covid-19/aAPC (modified aAPCs)	0,14,28 days (SC)	Phase 1 (NCT04299724)
	LV-SMENP-DC (modified DCs)	0,14,28 days (SC/IV infusion)	Phase 1-2 (NCT04276896)
Inactivated + alum vaccine	PiCoVacc	0, 14 days (IM)	Phase 3 (NCT04456595)
Whole- virion inactivated	BBV152	0, 14 days (IM)	Phase 1 -2 (NCT04471519)
Protein subunit	NVX-CoV2373 (Recombinant SARS CoV-2 glycoprotein NP vaccine with Matrix M)	0, 21 days (IM)	Phase 1 (NCT04368988)
Protein subunit	SCB 2019 (Native like Trimeric subunit Spike Protein vaccine)	0, 21 days (IM)	Phase 1 (NCT04405908)
	COVAX19 (recombinant spike protein with Advax-SM adjuvant)	1 dose (IM)	Phase 1 (NCT04453852)

Dr. ShwetaSurve*, Dr. NehaSawant* *Speciality Medical Officer, Department of Pharmacology

Challenge studies in COVID-19 vaccine development [11, 12]

Some researchers have proposed using a 'challenge study' to deliberately infect individuals to accelerate vaccine development. Challenge studies have aided the development of treatments and vaccines for malaria, influenza, typhoid fever, cholera, and dengue. Because these studies are undertaken in a controlled environment, it is easier for researchers to study natural disease progression than it would be in the field. In traditional vaccine trials, a high-risk population is usually studied, but not everyone in that population is necessarily exposed, and risk may not be evenly distributed; people's exposure to infection may vary, and not everyone may be infected during the trial. This means that large trials with substantial follow-up time to accumulate enough cases are needed to test vaccine efficacy.

A challenge study guarantees uniform exposure, so can be done faster with fewer participants. This approach could speed up vaccine development by eliminating ineffective candidates early on and accelerating field trials of the most promising vaccines. In the UK, a challenging study is already underway using related coronaviruses that cause milder disease. A major limitation of this approach is that results using other coronaviruses might not directly apply to SARS-CoV-2, the coronavirus that causes COVID-19. SARS-CoV-2 challenge studies could enable three things: studying clinical progression, developing effective vaccines, and testing candidate therapies. Candidate vaccines that have satisfied phase I safety and phase IIa dosage trials could be administered to volunteers who are subsequently challenged with the virus as part of a phase IIb trial to see how well the vaccine protects them as compared with a placebo or suitable alternative. Promising vaccines must eventually undergo large-scale testing in at-risk communities, but the process of assessing candidate vaccines before large phase III trials could be substantially accelerated by challenge studies. The stakes of a SARS-CoV-2 challenge study are high due to the risks of harm to participants. There may be devastating repercussions for all other human challenge studies if one or more volunteer participant(s) were to experience significant adverse outcomes or even death from intentional exposure to COVID-19. A SARS-CoV-2 challenge study should not just be well-designed with appropriate safeguards to minimize risk, but its inherent risks and its justification – seeking to more quickly reduce the human toll of the pandemic as a global good – should be communicated to the public to minimize potential fallouts.

Conclusion

As no effective treatment against SARS-CoV-2 is currently available, the best action is to develop vaccines to prevent the infection. Some potential vaccine candidates have progressed to Phase I and II clinical trials, but a year and a half are likely to pass before an effective vaccine is vetted through trials and is ready for marketing for humans. Therefore, considerable efforts should be given to limit or hinder the spread of the virus. Also, pandemics will generate simultaneous demand for drugs and vaccines around the world. The elderly and those with underlying diseases or chronic

comorbidities are at greater risk of severe disease or mortality. Clinical and serologic studies will be needed to confirm which populations remain at the highest risk once effective treatments or vaccines are available. Strong international coordination and collaboration among studies, pharmaceutical companies, regulators, and governments are needed to ensure that promising therapies or vaccines can be manufactured and supplied successfully. The COVID-19 pandemic has created devastating social, economic, and political threats. It is time for us to work together, share experiences, and move forward to fight against them. Although this virus persists, there is light at the end of the tunnel.

References

1. *Shih HI, Wu CJ, Tu YF, Chi CY. Fighting COVID-19: A quick review of diagnoses, therapies, and vaccines. Biomed J. 2020 Aug;43(4):341-354.*
2. *Graham BS. Rapid COVID-19 vaccine development. Science. 2020 May 29;368(6494):945-6.*
3. *Food and Drug Administration. Coronavirus (COVID-19) Update: FDA issues emergency use authorization for potential COVID-19 treatment. FDA News Release. 2020 [Internet] [cited on July 2020]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.*
4. *Ahmed SF, Qadeer AA, McKay MR. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. Viruses. 2020 Mar;12(3):254.*
5. *Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. New England Journal of Medicine. 2020 May 21;382(21):1969-73.*
6. *Funk CD, Laferrière C, Ardakani A. A snapshot of the global race for vaccines targeting SARS-CoV-2 and the COVID-19 pandemic. Frontiers in Pharmacology. 2020 Jun 19;11:937.*
7. *Khuroo MS, Khuroo M, Khuroo MS, Sofi AA, Khuroo NS. COVID-19 vaccines: A race against time in the middle of death and devastation! Journal of Clinical and Experimental Hepatology. 2020 Jun 10.*
8. *Le TT, Andreadakis Z, Kumar A, Roman RG, Tollefsen S, Saville M, Mayhew S. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020 Apr 9;19(5):305-6.*
9. *Pandey SC, Pande V, Sati D, Upreti S, Samant M. Vaccination strategies to combat novel corona virus SARS-CoV-2. Life Sciences. 2020 Jun 12:117956.*
10. *World Health Organization. DRAFT landscape of COVID-19 candidate vaccines. World. 2020 May 5.[Internet] [cited on July 2020]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.*
11. *Kathleen Doheny. Are Human Challenge Trials for COVID-19 Vaccine Worth the Risk? 2020 August 07. [Internet] [cited on July 2020]. Available from:https://www.medscape.com/viewarticle/935377.*
12. *Schaefer GO, Tam CC, Savulescu J, Voo TC. COVID-19 vaccine development: Time to consider SARS-CoV-2 challenge studies? Vaccine. 2020 Jul 14;38(33):5085-5088.*

SPONTANEOUSLY REPORTED CASES FOR DRUGS USED IN COVID-19

This is an excerpt from an update published by WHO in their report dated 23rd September 2020. The reference for the main publication is as follows:***Descriptive analysis of COVID-19 related spontaneous reports from VigiBase: interim results.Report date: 2020-09-23. [Internet]. [Last accessed on 27th Nov 2020].*** **Available:**https://www.who.int/medicines/regulation/medicines-safety/COVID19-PV-update12.pdf . This publication is solely in academic interest to disseminate the scientific information.

Descriptive analysis of COVID-19 related spontaneous reports from VigiBase: interim results is a twelfth review of global reporting of ADRs for drugs used to treat COVID-19 pandemic. For a few drugs, clinical trial results point to some efficacy in the disease. Among these, remdesivir is so far the only antiviral drug while glucocorticoids and the heparin class drugs have positive effects on complications of the disease. Other drugs widely used during the first part of the pandemic have by now been reported as ineffective in the patient groups studied, while numerous other suggested treatments still lack reliable information on their respective efficacy in COVID-19. The review has been adapted to the current state of knowledge and focus is hence given to remdesivir, the glucocorticoids and the heparin class of drugs for automated and manual reviews following the pattern of previous reviews. In addition, the COVID-19 related reporting into VigiBase for another two substances, favipiravir and ivermectin, has now passed the threshold of more than 100 reports. A full overview of the reporting for these drugs has also been included. Reports were considered for inclusion if they were received at the National Centres between November 1st 2019 and September 6th 2020 and were reported to VigiBase no later than September 6th.

The cumulative reports for various drugs has been tabulated below in Table 1.

Table 1: N_old display number of reports described in previous reports, which included reports received to VigiBase no later than the 17th of August. N_new includes number of reports received

Drug group	N_old	N_new	N_total
Azithromycin	1446	82	1528
Chloroquine	432	2	434
Hydroxychloroquine	2400	128	2528
Lopinavir;Ritonavir	803	69	872
Remdesivir	1975	43	2018
Tocilizumab	547	49	596
Heparin group substances	195	11	206
Oseltamivir	175	3	178
Sarilumab	158	1	159
Glucocorticoids group	217	34	251
Ivermectin	65	66	131
Favipiravir	81	22	103
Other drugs	496	37	533
Unique reports	6701	391	7092

to VigiBase no later than the 6th of September. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase.

Assessment of causality in individual cases is for all COVID-19 drugs difficult due to the background disease, the limited data on the drugs used in this disease and the relatively large proportion of multiple concomitant other COVID-19 treatments and has therefore in most cases not been performed.

Overview of Patient Characteristics

Cumulatively, a total of 7092 reports have been received from six WHO regions, namely the Region of the Americas (44%), European Region (37.6%), Eastern Mediterranean Region (11.5%), Western Pacific Region (4.6%), South-East Asia Region (2%), and African Region (0.2%). 57% of the reports were classified as “serious”. Males accounted for 56 % of the reports and females for 37.6 %. Figure one depicts patient characteristics for these drugs.

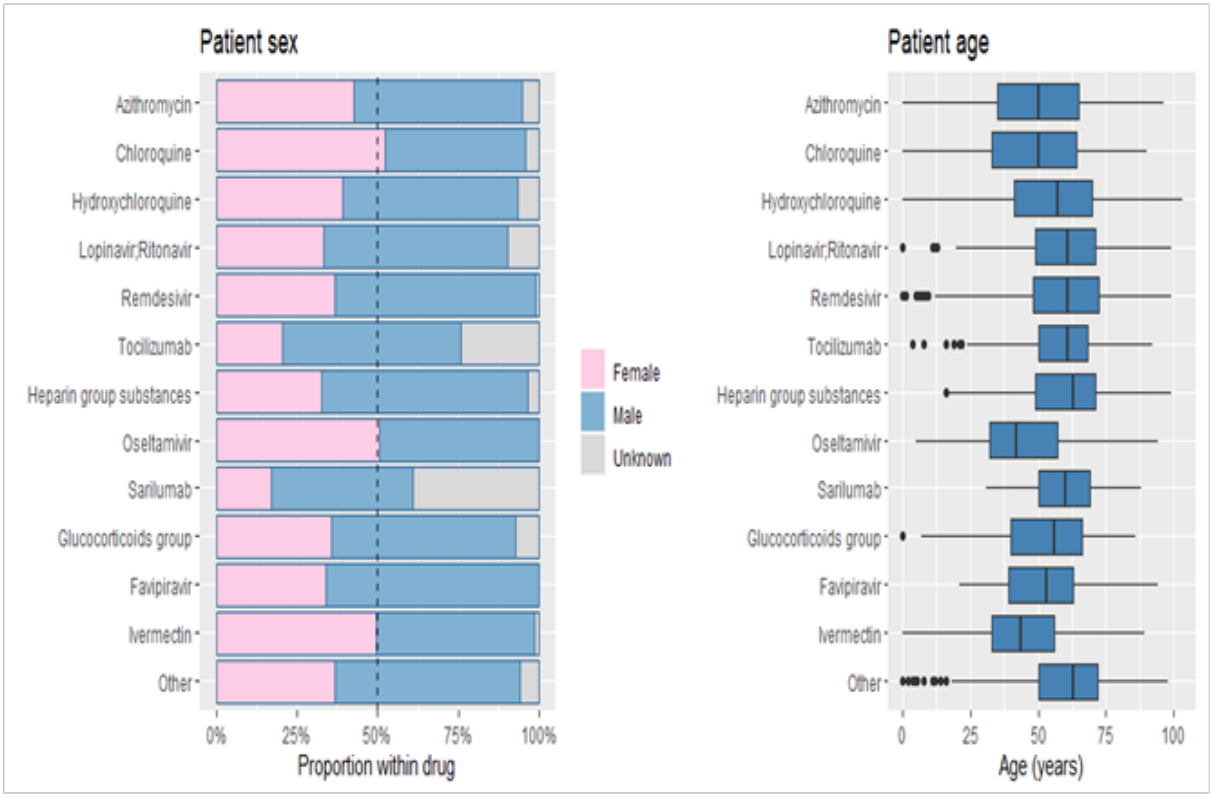

Figure 1: Figure on left shows counts of reports which include each drug as suspected or interacting. Reports, including several drugs will be counted once for each reported drug. Figure on the right shows patient age boxes show medians and interquartile ranges.

Remdesivir

There were 43 new reports for remdesivir during this reviewing period, adding up to a cumulative total of 2018 reports. The new reports included 34 men, eight women and one with unknown sex.The

new reports originated from the European Region (N=36), South-East Asia Region (N=3), Western Pacific Region (N=3) and Region of the Americas (N=1). The most frequently reportedCOVID-19 drugs co-administered with remdesivir were heparins (741), glucocorticoids (585), azathioprine (318) and tocilizumab (140).

The 43 new reports received for this period contain 52 preferred terms of which 11 are reported for the first time. These are pancreatitis acute, rash morbilliform, symmetrical drug-related intertriginous and flexural exanthema, dysgeusia, pulmonary imaging procedure abnormal, fungaemia, pseudomonas infection, hypogammaglobulinaemia, ill-defined disorder, acute myocardial infarction and thrombocytosis, each reported once. Acute pancreatitis is of interest since it was noted in the tenth review that other pancreatic terms had been reported. Twelve pancreatic terms have now been reported occurring in 12 reports. However, there is evidence that COVID-19 infection may also cause increased pancreatic enzymes and pancreatitis, so the reports require closer scrutiny to assess causality.

Glucocorticoid group (GCG)

There were 34 new reports for the glucocorticoids group (GCG) during this reviewing period, adding up to a cumulative total of 251 reports. The most common substances were prednisone, methylprednisolone and dexamethasone accounting for nearly 90% of these drugs. The new reports included 14 men and 20 women. The new reports originated from the region of the Americas (N=17), European Region (N=8), Eastern Mediterranean Region (N=7) and Western Pacific Region (N=2). In the new reports, the median age was 52 years. For the new reports, a glucocorticoid was the single suspected drug in six reports. Five cases of premature delivery, four of which in neonates and one in a mother have been reported. Birthweight was 0.93-1.05 kg where reported. Co-reported terms are such as would be clinically expected in prematurity. Co-reported drugs with a COVID-19 indication were, in all cases, hydroxychloroquine and azithromycin. The cases, all reported from the same national centre, contain little to no clinical description thereby precluding any further analysis.

Heparin group drugs

There were 11 new reports for the heparin group substances during this reviewing period, adding up to a cumulative total of 206 reports. Enoxaparin and heparin reports make up more than 95% of the reporting in the group. The new reports included six men and five women. The new reports originated from the European Region (N=6), Eastern Mediterranean Region (N=4) and Region of the Americas (N=1). In the new reports, the median age was 63 years. A substance from the heparin group was the single suspected drug in six of the new reports. The class has a well-established pre-COVID-19 profile regarding potential harms and benefits.

The most commonly reported MedDRA PTs for the group refer to off-label use related terms and labelled terms describing haemorrhages, haematological or hepatic events. Only one drug event combination, hypofibrinogenaemia was highlighted by the method as being reported significantly more often than expected compared to other COVID-19 drugs. In all the five reported cases, tocilizumab was present as a co-suspect drug for which the reaction is labelled. This finding has been reviewed previously in relation to the use of tocilizumab in COVID-19.

Ivermectin

There were 66 new reports for ivermectin during this reviewing period, adding up to a cumulative total of 131 reports. The new reports included 29 men, 35 women and two with unknown sex. The new reports all originated from the region of the Americas (N=66). In the new reports, the median age was 46 years. For the new reports ivermectin was the single suspected drug in 29 reports.

Among the top reported adverse reactions for all 131 individual case safety reports, we have gastrointestinal problems such as diarrhoea, abdominal pain, decreased appetite, vomiting and nausea, terms that are all labelled for the drug. Dizziness, headache, urine abnormality, visual impairment, anxiety and depression are other examples of top-reported terms for the drug. These terms are not labelled for ivermectin but may have been caused by the concomitantly reported drugs mentioned in the reports or the underlying disease.

Favipiravir

There were 22 new reports for favipiravir during this reviewing period, adding up to a cumulative total of 103 reports. The new reports included 15 men and seven women. The new reports originated from the European Region (N=14), Eastern Mediterranean Region (N=6) and South-East Asia Region (N=2). In the new reports, the median age was 49 years. For the new reports,favipiravir was the single suspected drug in 15 reports.

The most-reported MedDRA PTs have been: intentional product use issue, liver function test increased, nausea, rash, vomiting, electrocardiogram QT prolonged, hepatotoxicity, alanine aminotransferase increased, erythema, pruritus. Of the 22 new reports delivered to VigiBase during this reporting period eight included MedDRA PTs that had never been reported before. These PTs were: neutropenia, tachycardia, abdominal pain upper, constipation, hyperuricaemia, hyponatraemia, loss of consciousness.

****Disclaimer stated in the document: Data in the reports are not complete, and only a subset of the reports in the analysis, unfortunately, contained narratives precluding quality causality assessment. With limited data available at this stage of the pandemic and the uncertainty over other confounders (such as the underlying disease), this report is no more than a preliminary overview of cases and reported ADRs.*

Dr. Rajmohan Seetharaman, Dr. Jaisen Lokhande Deptment of Pharmacology, LTMMC & GH, Mumbai

A NARRATIVE REVIEW OF NEWLY APPROVED DRUGS FOR COVID-19

Dr. Rajmohan Seetharaman* Dr. Jaisen Lokhande**

**2nd year Resident 0000-0002-4605-2805 – ** Assistant Professor 0000-0001-5614-1804*
Department of Pharmacology, LTMMC & GH, Mumbai

Preprint DOI: 10.31219/osf.io/7f3qs

Abstract

COVID-19 disease is swiftly spreading over the globe. There were no specific approved drugs or therapies at the start of the pandemic. Hence, the management of these patients involves optimized supportive care. Researchers worldwide are analyzing the viral structure viruses' pathophysiology to develop new drugs and repurpose the currently approved drugs. Regulatory authorities worldwide, such as the USFDA, EMA, CDSCO, etc. are working closely with these scientists. They are expediting their efforts by providing advice, technical assistance, regulatory flexibility, and leveraging on scientific information from the trials conducted across various parts of the globe. These efforts have led to emergency use authorizations and restricted emergency use approvals of a few drugs, namely remdesivir, favipiravir, and 2% propofol emulsion for use in COVID-19 patients. The USFDA has revoked the approval of chloroquine and hydroxychloroquine. Many more new drugs are in the pipeline for their antiviral or immunomodulatory or other supportive mechanisms of action. These drugs are under the radar of regulatory authorities who are monitoring their efficacy and safety firmly as the world hopes to find a solution to combat this pandemic.

Keywords: *SARS-CoV-2, pandemic, regulatory authorities, accelerated approval, pharmacotherapy.*

Introduction

The coronavirus disease 2019 (COVID-19) pandemic which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which first emerged in Wuhan, China in December 2019 has advanced into a worldwide pandemic with 16,558,289 cases and 656,093 deaths being accounted for overall till July 29th 2020[1-3]. The symptoms of SARS-CoV-2 vary from an asymptomatic disease or mild fever, cough or pneumonia to extremely life-threatening complications acute respiratory distress syndrome and multi-system organ failure, which may ultimately result to death [4,5]. Wu C et al. and few other authors reported that elderly patients, immunocompromised patients and those with preexisting cardiovascular or respiratory conditions seem, by all accounts, to be at the highest risk for life-threatening complications.[6,7]

Multiple therapeutic options involving investigational new drugs and the repurposing of existing drugs have been explored for the management of COVID-19. The pharmacotherapy ranges from pre and post-exposure prophylaxis to targeting the replication cycle and immune medicated processes resulting in life-threatening complications.[8] Without a demonstrated effective therapy, current management includes supportive care with antibiotics, invasive and non-invasive oxygen support, and off-label use of drugs, which are now under investigation.[9]

Drug development is an expensive and timely process with a high attrition rate, which is unsatisfactory in setting to the current global emergency.[10] Therefore the United States Food and Drug Administration (USFDA) has propelled an emergency program for possible therapies known as the Coronavirus Treatment Acceleration Program (CTAP), which uses every possible method to evaluate investigational drugs and expedite the approval process for drugs showing promising efficacy and adequate safety.[11] The Drug Controller General of India (DCGI) has likewise offered several waivers for accelerating the procedure from fast track approval of a repurposed drug to waiving animal studies and offering various flexible pathways which would have otherwise taken several months.[12]

Stages of the replication cycle of SARS-CoV-2 as drug targets

SARS-CoV-2 is known to have four structural proteins, namely spike (S), envelope (E), membrane (M), and nucleocapsid (N), which encapsulates the single-stranded viral RNA. Spike is the protein that interacts with the host cell receptors, and it is cleaved into S1 and S2 by the host cell protease, such as transmembrane protease serine-2 (TMPRSS2). The function of S1 is to bind to the host cell surface receptor, whereas the role of S2 is to mediate membrane fusion.

Recent protein modeling studies of spike protein suggest that SARS-CoV-2 has a strong binding affinity to human angiotensin-converting enzyme-2 (ACE-2) receptors and likely uses them as a mechanism for cell entry. ACE-2 receptors are highly expressed in type II alveolar pneumocytes of the lungs. However, they are also present in various other extrapulmonary sites such as the heart, kidney, endothelium, and intestine. Previous studies in mice demonstrated that binding of SARS-CoV-2 spike protein to ACE-2 receptor down-regulates the receptor and thereby contributes to severe lung injury.

After uncoating, the genomic RNA of the SARS-CoV-2 acts on m-RNA using host cell ribosome for translation of the replicase poly-protein 1a and 1ab (pp1a and pp1ab). Autoproteolytic cleavage of these poly-proteins by the protease enzyme then produces several non-structural proteins, including RNA dependent RNA polymerase (RdRp), helicase, and non-structural proteins 3, 4 & 6. These non-structural proteins 3, 4 & 6 are responsible for anchoring the SARS-CoV-2 replication/ transcription complex through recruitment of intracellular endoplasmic reticulum membranes to form double-membrane vesicles (DMV). RdRp and helicase localize to DMV`s and drive the

production of subgenomic RNA`s (Sg RNA`s) from which structural and accessory proteins are produced in the next phase of translation.

Once synthesized, the transmembrane structural proteins S, M & E are inserted and folded in the endoplasmic reticulum (ER) and then transported to the ER-Golgi intermediate compartment (ERGIC). On the other hand, the N proteins bind to the viral genome RNA in the cytoplasm to form nucleocapsid. Once the final virion assembly occurs in the intermediate compartment, mature virions are released via smooth-walled vesicles by exocytosis.[13-14] Various drugs acting at different stages of this replication cycle have been explored and repurposed for the treatment of COVID-19 out of which various regulatory authorities have approved a few, which are as follows:

Remdesivir

It is a broad-spectrum antiviral (nucleotide analog prodrug) targeting the RNA dependent RNA polymerase.[15] FDA issued emergency use authorization (EUA) on May 1st 2020 for use in hospitalized adults or children with severe disease (defined as oxygen saturation [SpO2] 94% or lower on room air or requiring supplemental oxygen, extracorporeal membrane oxygenation or mechanical ventilation) and required the drug to be administered by a healthcare provider via I/V infusion in doses recommended by EUA. The EUA requires the healthcare facilities and healthcare providers administering Remdesivir to agree to precise obligatory record-keeping and reporting requirements (including adverse event reporting to FDA Med-Watch.[16-17] Remdesivir is currently being evaluated by European Medicines Agency's (EMA`s) Committee for Medicinal Products for Human Use (CHMP), for conditional marketing authorization for the treatment of COVID-19.[18] Pharmaceuticals and Medical Devices Agency; Japan approved it on May 7th 2020 based on article 14-3 of PMD act.[19] Considering the global emergency and unmet medical need for COVID-19 disease, Central Drugs Standard Control Organization (CDSCO) on June 21st 2020 has approved restricted emergency use of Remdesivirinjectableformulations for the treatment of patients with severe COVID-19 infection subject to various conditions and restrictions.[20]

Dosage: Recommended EUA dosage for adults and children weighing 40 kg or more: A loading dose of 200 mg by IV infusion on day 1, followed by maintenance doses of 100 mg by IV infusion once daily from day 2. Optimal duration of treatment not known. The recommended total treatment duration is ten days for patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO). For those not requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is five days. Extension of treatment may occur if the patient does not demonstrate clinical improvement for up to five additional days (i.e., up to a total treatment duration of ten days).

Recommended EUA dosage for children weighing 3.5 to less than 40 kg (using the lyophilized powder formulation only): A loading dose of 5 mg/kg by IV infusion on day 1, which is followed

by maintenance doses of 2.5 mg/kg by IV infusion once daily from day 2. Optimal duration of treatment not known. The recommended total treatment duration is ten days for patients requiring invasive mechanical ventilation and/or ECMO. For those not requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is five days. Extension of treatment may occur if the patient does not demonstrate clinical improvement for up to 5 additional days (i.e., up to a total treatment duration of 10 days).[21](Table I)

Chloroquine Phosphate and Hydroxychloroquine

These are antimalarial drugs which showed antiviral activities in various in vitro studies. Chloroquine increases the vacuolar and endosomal pH resulting in decreased functioning by inhibiting endocytosis and inhibiting vacuolar ATPase (vATPase) proton pump on the lysosomal surface. It acts as a zinc ionophore, which increases Zn2+ entry into the cell, which has shown to inhibit viral replication in in-vitro studies. It also competitively inhibits the binding of the spike protein to the sialic acid on the cell membrane's surface. The immunomodulatory effects theoretically promise anti-inflammatory benefits in the severe stages of COVID-19. Hydroxychloroquine has a similar mechanism of action as chloroquine phosphate. Hydroxyl analog of chloroquine with similar mechanisms of action and adverse effects; may have more favorable dose-related toxicity profile than chloroquine, but cardio-toxicity (e.g., prolonged QT interval) is a concern with both drugs.[22-25]

The DCGI has also approved the protocol which was recommended by the ICMR nationaltask force for restricted use in high-risk contacts.[26] FDA had issued a EUA on March 28th, 2020 that permitted distribution of the drug from the strategic national stockpile (SNS) for use only in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible. FDA also issued a safety alert regarding adverse cardiac effects and cautioned against the medical use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting.[27-29] Effective June 15th, 2020, FDA has revoked the EUA for chloroquine and hydroxychloroquine. The EUA was issued based on a review of new information and reevaluation of the available data. The FDA concluded that the original criteria for issuance of the EUA for these drugs are no longer met. FDA concluded that it is unlikely that chloroquine and hydroxychloroquine may be effective in treating COVID-19 on the basis of the totality of scientific evidence available, and considering the incoming reports of associated serious cardiac adverse events and several newly reported cases of methemoglobinemia in COVID-19 patients, the already known and potential benefits of chloroquine and hydroxychloroquine do not outweigh the known and potential risks associated with the use authorized by the EUA.[30]

Dosage: For the treatment of hospitalized adults and adolescents weighing 50 kg or more, the recommended dosage of chloroquine phosphate was 1 g on day 1, then 500 mg daily for 4- 7 days

of total treatment based on clinical evaluation and the proposed dosage of hydroxychloroquine was 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation. [31,32] (Table 1)

The basis for the FDA decision to revoke the EUA for hydroxychloroquine and chloroquine is summarized below:

1. Suggested hydroxychloroquine and chloroquine dosage regimens, as detailed in the EUA fact sheets for healthcare providers, are unlikely to produce an antiviral effect.

2. There have been no consistent replications of earlier observations of decreased viral shedding with hydroxychloroquine or chloroquine treatment. Recent data from a randomized controlled trial assessing the probability of negative conversion showed no difference between hydroxychloroquine and standard of care alone.

3. Current United States treatment guidelines do not recommend using chloroquine or hydroxychloroquine in patients hospitalized with COVID-19 outside of a clinical trial, and the guidelines issued by NIH now also recommend against its use outside a clinical trial.

4. Recent evidence obtained from a large, randomized, controlled trial showed no evidence of benefit in outcomes assessed, such as mortality or hospital length of stay or need for mechanical ventilation for hydroxychloroquine treatment in hospitalized patients with COVID-19.[30]

Favipiravir

It is a broad-spectrum antiviral. The active favipiravir-RTP selectively inhibits RNA polymerase and prevents replication of the viral genome.[33] Considering the global emergency and unmet medical need for COVID-19 disease, CDSCO June 21st 2020 has approved restricted emergency use of oral favipiravir tablets for mild to moderate COVID-19 infection subject to various conditions and restrictions under the brand name of "fabiflu".[20]

Dosage: Favipiravir was used at a dosage of 1600 mg twice daily on day 1, which was followed by 600 mg twice daily thereafter for 7–10 or 14 days in several open-label COVID-19 studies in China.[34,35] (Table 1)

Other antivirals under evaluation

Other antiviral drugs currently under investigation are baloxavir, HIV protease inhibitors (namely; lopinavir, atazanavir, darunavir, nelfinavir, saquinavir, and tipranavir), neuraminidase inhibitors (namely; oseltamivir and zanamivir) and umifenovir.[36-37]

SARS-CoV-2-Mediated Inflammatory Responses as drug targets

Studies carried out earlier suggest that the immune response in COVID-19 patients is two-phased. In moderate disease, immune cells produce inflammatory cytokines to reduce the viral load. During this stage, it might be beneficial to use therapies to stimulate the immune response. During severe stages, COVID-19 patients exhibit a high cytokine level or hyper inflammation, which may lead to severe pulmonary damage resulting in acute respiratory distress syndrome (ARDS). Reversing pulmonary damage is a significant hurdle in treating COVID-19, and ARDS is one of the leading causes of mortality in these patients.

The origin of cytokines involved in the SARS-CoV-2 related cytokine storm is yet to be determined as researchers have not entirely assessed the complete immune response. One theory related to the cytokine storm involves rapid viral replication, which leads to large scale cell pyro-apoptosis. The macrophages are then recruited into the lungs and will, in turn, amplify the inflammatory response. Studies comparing serum cytokines levels in infected individuals comprising of patients exhibiting marked symptoms and those with severe symptoms have shown increased levels of IL-6, IL-10, TNF-alpha, and soluble IL-2R receptor associated with disease severity. Another study examined patients with pneumonia comparing cytokines and chemokine`s in patients admitted in the intensive care unit (ICU) as compared to those who were not admitted in ICU`s. They found the IL-2, IL-7, G-CSF, IP-10, MCP-1, and MIP-1 are all elevated in the patients admitted in ICU`s.[38,39]

While the patient's own immune system may cause respiratory distress syndrome and multi-organ failure leading to the death of some patients, treatment strategies may not be as simple as using a broad anti-inflammatory drug. Broad anti-inflammatory drugs may impair the patient's ability to eliminate the viral pathogen and may make the patient more susceptible to secondary infection, which could worsen the outcome. Understanding the specific cytokines involved in the COVID-19 cytokine storm is essential for developing treatments. Hence based on the observations made by earlier studies multiple therapeutic options are being explored and repurposed to manage the cytokine storm induced by SARS-CoV-2 at the severe stage of COVID-19.[38,39] Currently immunomodulators are still under evaluation by various regulatory authorities with only one drug which is supportive for mechanical ventilation being approved by the USFDA which is as follows;

Itolizumab

It is a humanized recombinant anti-CD6 monoclonal antibody of IgG1 iso-type that binds to domain 1 of CD6, thereby immunomodulating human lymphocytes without interfering with the binding of CD6 to the activated leukocyte-cell adhesion molecule. CDSCO on July 11th2020 has approved Restricted Emergency Use of Itolizumab injection 25mg/5mL solution for the treatment of cytokine release syndrome (CRS) in moderate to severe ARDS (acute respiratory distress syndrome) patients due to COVID-19.[40] (Table I)

Dr. Rajmohan Seetharaman, Dr. Jaisen Lokhande Deptment of Pharmacology, LTMMC & GH, Mumbai

Propofol 2%, emulsion

It is a sedative-hypnotic. On May 8th, 2020 USFDA approved Propofol 2%, emulsion to maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19 who require mechanical ventilation in an intensive care unit (ICU) setting.[41](Table 1)

Table 1: A summary of newly approved drugs for COVID-19

Drug & mechanism of action	Approval date & approving regulatory body	Dosage & recommended duration of therapy	Indication
1) Remdesivir (Broad-spectrum antiviral targeting the RNA dependent RNA polymerase)	1) May 1st 2020: USFDA 2) May 7th 2020: PMDA, Japan 3) June 21st 2020: CDSCO, India	1) Adults and children weighing 40 kg or more: 200mg I/V day 1, 100 mg I/V day 2 onwards. Recommended duration: 5-10 days. 2) Children weighing 3.5 to <40 kg: 5mg/kg I/V day 1, 2.5 mg/kg I/V day 2 onwards. Recommended duration: 5-10 days.	Hospitalized adults or children with severe COVID-19 infection
2) Chloroquine Phosphate and Hydroxychloroquine (antiviral and anti-inflammatory effects)	1) Approval: March 28th, 2020, USFDA 2) Revoked approval: June 15th, 2020	1) Chloroquine Phosphate: 1 g oral on day 1, 500 mg oral daily day 2 onwards. Recommended duration: 4-7 days. 2) Hydroxychloro-quine: 800mg oral on day 1, 400 mg oral daily day 2 onwards. Recommended duration: 4-7 days.	Adults and adolescents weighing 50 kg or more hospitalized with COVID-19 (for whom a clinical trial is not available or participation not feasible).
3) Favipiravir (Broad-spectrum antiviral selectively inhibits RNA polymerase)	June 21st 2020: CDSCO, India	1600 mg oral twice daily on day 1, 600 mg oral twice daily day 2 onwards. Recommended duration: 7-10 days.	Mild to moderate COVID-19 infection
4) Itolizumab (Humanized recombinant anti-CD6 monoclonal antibody)	July 11th 2020: CDSCO, India	25mg/5mL I/V	Cytokine release syndrome (CRS) in moderate to severe ARDS due to COVID-19
5)Propofol 2%, emulsion (sedative-hypnotic)	May 8th, 2020, USFDA	2%, emulsion, I/V	To maintain sedation via continuous infusion in patients greater than 16 years old with suspected or confirmed COVID-19 who require mechanical ventilation in the ICU

Other immunomodulators under evaluation

Immunomodulators currently under investigation include anakinra, baricitinib, colchicine, systemic corticosteroids (dexamethasone, hydrocortisone, methylprednisolone, and prednisolone), inhaled corticosteroids (ciclesonide), interferons (namely; IFN beta-1a. IFN beta-1b, IFN alfa, and Peginterferon lambda-1a), ruxolitinib, sarilumab, siltuximab,sirolimus, and tocilizumab.[36,37]

Other drugs and therapies under evaluation

Other drugs under evaluation include azithromycin, ascorbic acid, epoprostenol (inhaled), nitric oxide (inhaled), Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARBs), anticoagulants, COVID-19 convalescent plasma, famotidine, HMG-CoA reductaseinhibitors (statins), immune globulin (IGIV, IVIG, gamma-globulin), ivermectin, nebulized drugs, niclosamine, nitazoxanide, nonsteroidal anti-inflammatory agents (namely; ibuprofen and indomethacin), a tissue plasminogen activator (t- PA; alteplase) and Chinese herbal medicines.[36,37]

Conclusion

The COVID-19 pandemic presents the most significant crisis for public health and the world economy in the last 100 years. Numerous drugs have been used clinically after learning from severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), with ongoing clinical trials evaluating their efficacy and safety. Few novel therapies have also been proposed after taking into consideration the unique viral structure and distinct pathogenesis. We hope that a portion of these drugs breeze through the assessment of regulatory authorities in the coming months and strengthen the global healthcare system in their battle against this pandemic.

References

1. *Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E. Compassionate use of remdesivir for patients with severe Covid-19. New England Journal of Medicine. 2020 Apr 10.*
2. *Spinelli A, Pellino G. COVID-19 pandemic: perspectives on an unfolding crisis. Br J Surg. 2020 Mar 19;10.*
3. *WHO COVID-19 Dashboard [Internet]. Covid19.who.int. 2020 [cited 5 May 2020]. Available from: https://covid19.who.int*
4. *Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, Liu X, Wei L, Truelove SA, Zhang T, Gao W. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. The Lancet Infectious Diseases. 2020 Apr 27.*
5. *Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R,*

Holguin-Rivera Y, Escalera-Antezana JP, Alvarado-Arnez LE, Bonilla-Aldana DK, Franco-Paredes C, Henao-Martinez AF, Paniz-Mondolfi A. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel medicine and infectious disease. 2020 Mar 13:101623.

6. *Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine. 2020 Mar 13.*
7. *Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. The Lancet. 2020 Mar 28;395(10229):1014-5.*
8. *Wu R, Wang L, Kuo HC, Shannar A, Peter R, Chou PJ, Li S, Hudlikar R, Liu X, Liu Z, Poiani GJ. An update on current therapeutic drugs treating COVID-19. Current Pharmacology Reports. 2020 May 11:1.*
9. *Peng F, Tu L, Yang Y, Hu P, Wang R, Hu Q, Cao F, Jiang T, Sun J, Xu G, Chang C. Management and treatment of COVID-19: the Chinese experience. Canadian Journal of Cardiology. 2020 Apr 17.*
10. *Lythgoe MP, Middleton P. Ongoing clinical trials for the management of the COVID-19 pandemic. Trends in Pharmacological Sciences. 2020 Apr 9.*
11. *Coronavirus Treatment Acceleration Program (CTAP) [Internet]. U.S. Food and Drug Administration. 2020 [cited 22 June 2020]. Available from: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap*
12. *CDSCO: Rapid response regulatory framework for COVID-19 [Internet]. Cdsco.gov.in. 2020 [cited 22 June 2020]. Available from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTc4Mw==*
13. *Astuti I. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Apr 18.*
14. *Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virology journal. 2019 Dec;16(1):1-22.*
15. *Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, GÃ¶tte M. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. Journal of Biological Chemistry. 2020 May 15;295(20):6785-97.*
16. *US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of remdesivir for the treatment of hospitalized 2019 coronavirus disease (COVID-19)*

patients. 2020 May 1. From FDA website. (https://www.fda.gov/media/137564/download)

17. *US Food and Drug Administration. Fact sheet for health care providers: Emergency use authorization (EUA) of remdesivir (GS-5734). Revised 2020 Jun. From FDA website. (https://www.fda.gov/media/137566/download)*
18. *EMA receives application for conditional authorisation of first COVID-19 treatment in the EU - European Medicines Agency [Internet]. European Medicines Agency. 2020 [cited 22 June 2020]. Available from: https://www.ema.europa.eu/en/news/ema-receives-application-conditional-authorisation-first-covid-19-treatment-eu*
19. *PMDA's Efforts to Combat COVID-19 | Pharmaceuticals and Medical Devices Agency [Internet]. Pmda.go.jp. 2020 [cited 22 June 2020]. Available from: https://www.pmda.go.jp/english/about-pmda/0002.html*
20. *Approval of Favipiravir Tablets to Glenmark Pharmaceuticals and Remdesivir Injection to Cipla Ltd and Hetero Drugs [Internet]. Cdsco.gov.in. 2020 [cited 22 June 2020]. Available from: https://www.cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NjAwOA==*
21. *US Food and Drug Administration. Fact sheet for health care providers: Emergency use authorization (EUA) of remdesivir (GS-5734). Revised 2020 Jun. From FDA website. (https://www.fda.gov/media/137566/download)*
22. *Devaux CA, Rolain JM, Colson P et al. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?.Int J Antimicrob Agents. 2020; :105938. (PubMed 32171740) (DOI 10.1016/j. ijantimicag.2020.105938)*
23. *Colson P, Rolain JM, Lagier JC et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020; :105932. Editorial. (PubMed 32145363) (DOI 10.1016/j. ijantimicag.2020.105932)*
24. *Rolain MJ, Colson, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents. 2007; 30:297-308. (PubMed 17629679) (DOI 10.1016/j.ijantimicag.2007.05.015)*
25. *Chloroquine and hydroxychloroquine: Current evidence for their effectiveness in treating COVID-19 [Internet]. CEBM. 2020 [cited 22 June 2020]. Available from: https://www.cebm.net/covid-19/chloroquine-and-hydroxychloroquine-current-evidence-for-their-effectiveness-in-treating-covid-19/*
26. *Advisory on the use of Hydroxychloroquine [Internet]. Mohfw.gov.in. 2020 [cited 22 June 2020]. Available from: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf*
27. *US Food and Drug Administration. Letter of authorization: Emergency use authorization*

for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 Coronavirus disease. 2020 Mar 28. From FDA website. (https://www.fda.gov/media/136534/download)

28. *US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of chloroquine phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 27. From FDA website. (https://www.fda.gov/media/136535/download)*

29. *US Food and Drug Administration. FDA drug safety communication: FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. April 24, 2020. Available at https://www.fda.gov/media/137250/download.*

30. *US Food and Drug Administration. Letter regarding revocation of emergency use authorization (EUA) for emergency use of chloroquine phosphate and hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of Coronavirus disease 2019. 2020 Jun 15. Available at https://www.fda.gov/media/138945/download*

31. *U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Jun 15. Available at https://www.clinicaltrials.gov/.*

32. *Chen J, Liu D, Liu L et al. [A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19]. J Zhejiang Univ. 2020; 49:215-19. (PubMed 32391667) (DOI 10.3785/j.issn.1008-9292.2020.03.03).*

33. *De Clercq E. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chem Asian J. 2019;14:3962–3968. PMID: 31389664 DOI: 10.1002/asia.201900841*

34. *McGrane V. Massachusetts to launch first US trial of Japanese coronavirus drug. Boston Globe. Updated 2020 Apr 15. Accessed 2020 Apr 14. Available at: https://www.bostonglobe.com/2020/04/07/metro/massachusetts-launch-first-trial-japanese-covid-drug.*

35. *Cai Q, Yang M, Liu D et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering (Beijing). 2020. PMID: 32346491 DOI: 10.1016/j.eng.2020.03.007*

36. *Wu R, Wang L, Kuo HC, Shannar A, Peter R, Chou PJ, Li S, Hudlikar R, Liu X, Liu Z, Poiani GJ. An update on current therapeutic drugs treating COVID-19. Current Pharmacology Reports. 2020 May 11:1.*

37. *Assessment of Evidence for COVID-19-Related Treatments [Internet]. Ashp.org. 2020 [cited 22 June 2020]. Available from: https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx*

38. *Sun X, Wang T, Cai D, Hu Z, Liao H, Zhi L, Wei H, Zhang Z, Qiu Y, Wang J, Wang A. Cytokine*

storm intervention in the early stages of COVID-19 pneumonia. Cytokine & Growth Factor Reviews. 2020 Apr 25.

39. *Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal Transduction and Targeted Therapy. 2020 May 29;5(1):1-0.*

40. *Biocon's Breakthrough Drug Itolizumab Receives DCGI Nod for Emergency Use in Moderate to Severe COVID-19 Patients [Internet]. Biocon.com. 2020 [cited 30 July 2020]. Available from: https://www.biocon.com/docs/Biocon_PR_Itolizumab_Approved_for_Covid_India.pdf*

41. *FDA emergency use authorisation: Fresenius KabiPropoven 2% [Internet]. Fda.gov. 2020 [cited 22 June 2020]. Available from: https://www.fda.gov/media/137888/download*

Dr NitashaKeswani, Second year resident, Department of Pharmacology, LTMMC&GH, Mumbai

SAFETY ALERTS FOR DRUGS USED IN COVID-19

Dr NitashaKeswani

Second year resident, Department of Pharmacology, LTMMC&GH, Mumbai

FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems

Hydroxychloroquine and chloroquine have not been shown to be safe and effective for treating or preventing COVID-19. FDA authorized their temporary use during the COVID-19 pandemic for treatment of the virus in hospitalized patients when clinical trials are not available, or participation is not feasible, through an Emergency use authorization (EUA).

Hydroxychloroquine and chloroquine can cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia. These risks may increase when these medicines are combined with other medicines known to prolong the QT interval, including the antibiotic azithromycin, which is also being used in some COVID-19 patients without FDA approval for this condition. Patients who also have other health issues such as heart and kidney disease are likely to be at increased risk of these heart problems when receiving these medicines.

Reference: FDA cautions use of hydroxychloroquine/chloroquine for COVID-19. U.S. Food and Drug Administration 2020. [Internet] [cited 1 July 2020]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

FDA Warns of Newly Discovered Potential Drug Interaction That May Reduce Effectiveness of a COVID-19 Treatment Authorized for Emergency Use

Co-administration of remdesivir and chloroquine phosphate or hydroxychloroquinesulfate is not recommended as it may result in reduced antiviral activity of remdesivir. The agency is not aware of instances of this reduced activity occurring in the clinical setting but is continuing to evaluate all data related to remdesivir.

Reference: FDA cautions use of hydroxychloroquine/chloroquine for COVID-19. U.S. Food and Drug Administration 2020. [Internet] [cited 1 July 2020]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

Dr NitashaKeswani, Second year resident, Department of Pharmacology, LTMMC&GH, Mumbai

European Medicines Agency. EMA gives advice on the use of non-steroidal anti-inflammatories for Covid-19.

In 2019, the EMA's Pharmacovigilance Risk Assessment Committee began a review of ibuprofen and ketoprofen following claims that these drugs could worsen chickenpox and some bacterial infections. The summaries of product characteristics for several NSAIDs already include a warning that these drugs may mask the signs or symptoms of a worsening infection.The UK Medicines and Healthcare products Regulatory Agency (MHRA) has reported that there is currently no research into the link between ibuprofen and the likelihood of contracting SARS-CoV-2, or the link between ibuprofen and the worsening of Covid-19 symptoms. The MHRA has advised patients to take paracetamol to treat the symptoms of Covid-19, unless paracetamol is not suitable for them. People who have been advised to use ibuprofen by a healthcare professional should not stop taking it.

Reference: EMA advice on the use of NSAIDs for Covid-19 Drug and Therapeutics Bulletin 2020; 58:69.

Two Major Coronavirus Vaccine Trials Have Restarted After Being Paused for Safety Investigations

Pharmaceutical companies running clinical trials for two high-profile coronavirus vaccine candidates resumed, after safety investigations found that serious illnesses in volunteers did not appear to be related to the vaccines. AstraZeneca's trial, which is being conducted in a partnership with the University of Oxford in the UK, has been halted twice. The first pause occurred after a patient in July developed multiple sclerosis, which was determined to be unrelated to the vaccine. The trial was paused again in September after a participant developed a neurological illness called transverse myelitis.

Reference: Johnson & Johnson And AstraZeneca Resume COVID Vaccine Trials. Buzzfeednews.com. Published on 24th October 2020 [Internet] [cited 1 November 2020] Available from:https://www.buzzfeednews.com/article/azeenghorayshi/astrazeneca-johnson-johnson-vaccine-trials-safety .

Dr. AbhilashaRashmi, Dr.ww SharmadaNerlekar, Department of Pharmacology, LTMMC & GH, Mumbai.

CROSSWORD PUZZLE ON COVID-19

Dr. AbhilashaRashmi*,Dr SharmadaNerlekar*

**Associate Professor, Department of Pharmacology, LTMMC & GH, Mumbai.*

	1R	9E		11D						16R
			2A			12I			L	
	8T									
								15E		
3R				V		13R				L
							4	R		17C
			10							
5	U		I				14			
					6H					O
							D			
					7S					E

ACROSS

1. _____, a monophosphoramidateprodrug of an adenosine analogue, is a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells.

2. Umifenovir, also known as_____, is a promising repurposed antiviral agent with a unique mechanism of action targeting the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope.

3. High doses of this guanine analogue _____used in the SARS trials resulted in hemolyticanemia in more than 60% of patients.

4. Raised____ acids, diarrhea, elevated transaminases and reduction in neutrophil count are some important adverse reactions found with Favipiravir, which inhibits the RNA polymerase, halting corona viral replication.

5. Along with immunomodulatory effects, Chloroquine and hydroxychloroquine appear to block viral membrane_____ & endocytosis by multiple mechanisms.

6. _____toxicity is the major adverse reaction seen with Tocilizumab, a monoclonal antibody IL-6 receptor antagonist. re

Dr. AbhilashaRashmi, Dr.ww SharmadaNerlekar, Department of Pharmacology, LTMMC & GH, Mumbai.

7. Camostatmesylate, an approved agent in Japan for the treatment of pancreatitis, prevents novel coronavirus cell entry in vitro through inhibition of the host _____ protease.

DOWN

8. _____ is FDA approved to treat cytokine release syndrome following chimeric antigen receptor T-cell therapy. So, it has been used in small series of severe COVID-19 cases with reports of success.

9. The first clinical use of Remdesivir was for the treatment of _____virus disease.

10. _____effectively inhibits the RNA-synthesizing activity of nidoviruses (including SARS-CoV) in vitro, probably by directly affecting template binding.

11. An RCT of _____/cobicistat in China isgoing on because vitro cell models have demonstrated proteolytic activity of _____against SARS-CoV-2.

12. Monoclonal antibodies like Tocilizumab and Sarilumab prevent ____receptor activation and inhibits its signaling also.

13. Conventionally used in the treatment of malaria, SLE and ___, Chloroquine and Hydroxychloroquine also block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification.

14. One of the common adverse effects of Chloroquine and Hydroxychloroquine are hematologic effects including hemolysis with _____deficiency.

15. The novel mechanism that Camostatmesylate prevents nCoV cell _____has provided an additional drug target for future research.

16. In the _____pigment epithelium, accumulation of chloroquine causes a toxic lesion known as a “bull’s-eye” maculopathy, which is associated with a decrease in visual acuity.

17. The key step transforming mild COVID disease to severe is immune dysfunction and _____dysregulation resulting in what is called as “_____ storm syndrome”.

Answers:

1.Remdesivir 2. Arbidol 3. Ribavirin 4.Uric acid 5. Fusion 6. Hepato 7. Serine 8. Tocilizumab 9. Ebola 10. Zinc 11.Darunavir 12. IL-6 13. RA 14. G6PD 15. Entry 16. Retinal 17. Cytokine.

Dr. Abhilasha Rashmi, Dr. Sharmada Nerlekar, Department of Pharmacology, LTMMC & GH, Mumbai.

MATCH THE ADVERSE EFFECT WITH THE DRUG

***DrAbhilashaRashmi, *DrSharmadaNerlekar**

**Associate Professor, Department of Pharmacology, LTMMC & GH, Mumbai.*

1	Ivermectin	A	N-methyl-D-Aspartate receptor antagonist
2	Favipiravir	B	Nucleoside RNA polymerase inhibitor
3	Fusogenix DNA Vaccine	C	Prevents Cytotkine storm
4	Gimsilumab	D	Anti IL-6 receptor
5	AT-100	E	Defensin mimetic drug
6	Ifenprodil	F	Single dose intranasal Vaccine for COVID-19
7	mRNA-1273 vaccine	G	Initial use –Idiopathic pulmonary Fibrosis
8	Brilacidin	H	P2X3 Receptor Antagonist
9	Leronlimab	I	DestabilisesImportinalfa& Importin Beta
10	Galidesivir	J	Novel human recombinant protein
11	Tocilizumab	K	CCR-5 antagonist
12	AdCOVID	L	Entos pharmaceuticals
13	Sarilumab	M	Targets Spike (s) protein
14	Pirfenidone	N	Targets GM-CSF
15	Gefapixant	O	First approved Coronavirus drug in China

Answers:

1. I;	2. O	3.L	4. N	5. J	6. A	7. M	8. E	9. K	10. B	11. C	12. F
13. D	14. G	15. H									

We would like to request all the departments to contribute in ADR reporting.

Please feel free to contact us for the same.

Names	Extn. No.	E-mail
Dr. Sudhir Pawar	3162	dr.sudhirpawar@gmail.com
Dr. Neha Kadhe	3206	nehakadhe@yahoo.com
Dr. Manjari Advani	3205	manjari.advani@gmail.com
Dr. Jaisen Lokhande	3165	dr_jaisen@yahoo.co.in
Dr. Swati Patil	3165	drswati246@gmail.com
Dr. Hardik Thaker	3160	drhardikthaker@gmail.com
Dr. Prajakta Kude	3160	prajakta.kude13@gmail.com
Dr. Shankhini Deshpande	3160	shankhinid@gmail.com
Dr. Shariva Ranadive	3160	ranadiveshariva@gmail.com
Dr. Prathamesh Avhad	3160	prathiavhad@gmail.com

Address for correspondence :

Department of Pharmacology,
College Building, LTMMC & LTMGH,
Sion, Mumbai 400 022.
Tel.: 022-2406 3160 • E-mail: ltmghbulletin@gmail.com

Printing and distribution of this bulletin is sponsored by

ALKEM LABORATORIES LIMITED

BOEHRINGER - INGELHEIM

GLAXOSMITHKLINE

GLENMARK PHARMACEUTICALS LIMITED

NOVARTIS INDIA LTD.