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OFF LABEL AND INVESTIGATIONAL THERAPIES FOR COVID-19 PATIENTS

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ABSTRACT

There was no specific vaccine or successful treatment for this rapidly spreading and life-threatening viral respiratory infection in December of last year when COVID-19 emerged. Clinical trials have been planned and are underway to examine whether drugs used for influenza, HIV and other viruses, as well as antihelmintics (ivermectin) and antimalarials (chloroquine, hydroxychloroquine) that demonstrate in vitro antiviral activity, are successful and safe for Covid-19. No compelling evidence exists so far that these antiviral and anti parasitic drugs are of some interest to Covid-19. Notwithstanding the absence of clinical efficacy evidence, these medications are commonly used for prophylaxis and treatment of this viral infection outside of clinical trials (off label). This practice has been termed as off-label usage and is legal provided that the same has been approved by national laws and regulations. In conclusion, the COVID-19 pandemic is a global issue and needs unparalleled global solutions, as we will not allow people to die from complications related to the disease.

Keywords: Antihelmintics, Antimalarials, Anti parasitic, COVID-19, Prophylaxis

INTRODUCTION

Off-label drug use applies, in terms of dosage, patient age, route of administration, indications and contra-indications, to the use of medications outside the provisions of the product license. Off-label drug use is relatively common in medical practice, even though solid clinical evidence sometimes does not support it. Off-label prescription of a medication is usually legal, but the marketing by a drug manufacturer of off-label uses is considered illegal as the manufacturer does not fully

understand. Any off-label prescriptions should be allowed to enable doctors to take good care of patients and provide them with certain treatment choices, but such prescriptions should remain an exception to the rule and should be scrutinized and regulated using well-defined mechanisms by regulatory agencies. Marketing authorizations for medicinal products are issued on the basis of their efficacy for particular indications, as assured by a positive benefit-risk ratio in clinical trials. This makes it difficult for a medication to be licensed for all indications, dosage forms, routes of administration, and all age ranges (such as children, pregnant women and lactating mothers). It allows the trend of off-label use widespread in the world **[1]**.

Ground reality & Off-label use

As of now, none of the used pharmaceutical drugs have been shown to be safe and effective in treating the disease in the current pandemic. However in the care of patients, a wide variety of pharmaceutical products have been used and the process of using the same in clinical trials is also under way. In other words, medicines which have not yet been licensed by the national drug regulatory authorities for the treatment of COVID-19 disease are used in different countries **[2]**. This practice has been referred to as off-label use and is legal provided that the same has been licensed by national laws and regulations, and so it is a must for all health practitioners to be informed of the same and not for everyone, but only for those cases that really need drug intervention.

In addition, the issues of unnecessary stocking or unavailability of the drug for its primary indication must be avoided due to the pattern of off-label use of a medicine prescribed primarily for any other condition. It must be recognized that without waiting for the results of clinical trials, the use of drugs on an emergency basis can be considered ethical, as long as no existing successful treatment is available. It is not possible to initiate clinical trials promptly; the fact that either patients or their legal representatives have given informed consent; the therapeutic off-label use is strictly monitored; and the outcomes of the treatment received are carefully reported and communicated on a timely basis with the medical fraternity.

It is necessary to bear in mind that the decision to provide unproven care is strictly based on the agreement reached between the reported case and the treating physician, given that the national regulations, have already been accepted. The intention should however be to provide this procedure as part of clinical trials in order to potentially benefit the scientific community, but all this would depend on the approval of the patients or their families. In all cases, in

order to draw accurate conclusions on safety, effectiveness, possible risks and the associated benefits, treatment strategies showing promising results have to be further explored in a clinical trial.

OFF LABEL DRUGS BENEFITS FOR PATIENTS

It is not forbidden to prescribe off-label medications, nor does it generally mean unreasonable pharmacotherapy. Physicians, nevertheless, must be mindful that they assume full responsibility for any adverse effects on their patients while administering an unapproved medication, even though patients have signed an Informed Consent document. Doctors, but not their patients, are believed to be entirely capable of assessing the chances of adverse effects against the possible benefits of the treatment prescribed **[3]**.

Off-label use is targeted at helping a particular patient. It is important to remember that the word "off-label" does not mean abuse, illegal, contraindicated, or investigational use. Off-label use will provide a patient with the best possible intervention, as well as the quality of treatment for a specific health condition for which there is no relief from the standard medications primarily suggested for its management. Without a certain amount of off-label prescribing, medical treatment may be challenging in oncology, pediatrics, geriatrics, obstetrics, and other practice areas. If empirical and medical evidence justifies off-label applications, doctors assist patients by administering off-label items.

If drug efficacy remains unproven and thus unknown for Covid-19, even small risks of adverse reactions must be taken seriously into account. In addition, when prescribing off-label medications for prophylaxis and/or asymptomatic or mild Covid-19, doctors should bear in mind that even if the medication were potentially successful, clinical benefits would be marginal or non-existent for most treated patients. Most (80%) Covid-19 patients are expected to experience mild to moderate symptoms with spontaneous resolution of infection, whereas about one-fifth (20%) develop severe respiratory symptoms and acute respiratory distress syndrome (ARDS). In about 6.1 percent of all infected patients, the symptoms of the disease intensify dramatically to the degree that mechanical ventilation is required. It should also be borne in mind that risks of adverse drug events that may be deemed tolerable for patients with serious illness could not be appropriate for those with only moderate symptoms and who are likely to progress to spontaneous healing **[4]**.

Solidarity trial

To date, more than 90 countries have agreed to be part of a multi-national solidarity trial in this respect, which will be

funded by the World Health Organization and the participating countries. The purpose of this trial is to identify the medicines in this ongoing fight that can save the lives of humans. As of now it has been determined to test the efficacy of four different medications or their combinations and equate them with the standard medication currently used **[5]**.

Treatment modalities

At the same time, a wide variety of care methods in various nations have been used in heterogeneous environments. In fact, the use of hydroxychloroquine has been associated with a substantial decrease in viral load in a nonrandomized clinical trial, and these findings are also confirmed by azithromycin. In India, the combination of lopinavir and ritonavir has been approved by national authorities, but off-label use of hydroxychloroquine and azithromycin has also been recommended for use in critical patients or those needing intensive care unit management **(Table 1)**.

Table 1: List of drugs used for treatment of COVID-19

S. No	Name of the Drug	Uses	Treatment for Covid-19	References
1.	Hydroxychloroquine and Azithromycin	anti-malaria drug and macrolide antibacterial drug	Results showed that within 6 days of treatment, all patients taking the mixture were virologically healed.	[6]
2.	Dexamethasone	anti-inflammatory drug	Studies have found that it reduces the risk for deaths by about 30% for people on ventilators and by about 20% for people who needed supplemental oxygen.	[7], [8]
3.	Remdesivir	anti-viral drug	Has Emergency Use authorization for treatment of moderate to severe COVID-19 patients.	[7], [8]
4.	Tocilizumab	rheumatoid arthritis	Licensed for the treatment of mild to serious COVID-19 patients as a 'Off-label' drug.	[7]
5.	Itolizumab	treatment of Psoriasis	Has got Emergency Use Authorization for treatment of moderate to severe COVID-19 patients.	[7]
6.	Favipiravir	antiviral drug	mild to moderate COVID-19 patients in India.	[7]
7.	Sarilumab	Interleukin-6 (IL-6) receptor antagonist	Potential therapy of patients seriously ill with COVID-19 for acute respiratory distress syndrome (ARDS).	[7]

Remdesivir is a broad-spectrum antiviral drug that has antiviral activity. On October 22, 2020, under the brand name Veklury, the FDA approved remdesivir for the care of hospitalized COVID-19 patients aged 12 years and older.

Bamlanivimab (LY-CoV555) is a human IgG1 monoclonal antibody (mAb) recombinant neutralizing agent directed

against the SARS-CoV-2 spike protein. On November 9, 2020, FDA Emergency Use Permission was issued for the treatment of newly diagnosed COVID-19.

Casirivimab and Imdevimab (REGN-COV2) are a mixture of two monoclonal antibodies primarily intended to suppress SARS-CoV-2 virus infectivity. On November 21, 2020, FDA Emergency Use Permission was issued for the treatment of mild to moderate COVID-19.

INVESTIGATIONAL THERAPIES [9]

Baricitinib Phase 3 trials to assess the efficacy of a Janus kinase (JAK) inhibitor called baricitinib (marketed under the brand name Olumiant for the treatment of rheumatoid arthritis) in the treatment of patients with COVID-19 are currently in progress. Eli Lilly announced the FDA Emergency Use Authorization of baricitinib in conjunction with remdesivir for use in hospitalized COVID-19 patients on November 19, 2020.

Bemcentinib In a UK Phase II clinical trial, an AXL kinase inhibitor named bemcentinib has been rapidly monitored to study its efficacy in the treatment of hospitalized patients with COVID-19. Bemcentinib has been tested previously in patients with cancer and has been shown to be safe and well-tolerated. Strong antiviral activity against several enveloped viruses, including Ebola and Zika viruses has also been documented in preclinical models and has been extended to include SARS-CoV-2 in recent evidence.

Bevacizumab A VEGF inhibitor called bevacizumab (marketed under the brand name Avastin for certain types of cancer) being studied as a treatment for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in critically ill patients with COVID-19 pneumonia at the Qilu Hospital of Shandong University in Jinan, China.

Convalescent Plasma An emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 was released by the FDA on August 23, 2020. The FDA decided that it is safe to assume that convalescent COVID-19 plasma could be effective in reducing the severity or shortening the duration of patients with COVID-19 disease hospitalized with COVID-19.

Dexamethasone According to researchers at the University of Oxford in England, the affordable and readily available steroid dexamethasone decreased the risk of death among critically ill COVID-19 patients by up to one third. The medicine did not seem to benefit patients with less acute illnesses.

EIDD-2801 A team of UNC-Chapel Hill researchers are optimistic that a large oral antiviral spectrum called EIDD-2801 may be used as a possible prophylactic or therapy for COVID-19 and other corona viruses. EIDD-2801 has been approved by

Ridgeback Biotherapeutics and has obtained permission from the FDA to begin patient trials. Ridgeback Biotherapeutics and Merck have entered into a collaboration agreement to grow EIDD-2801 on May 26, 2020.

Favipiravir Also approved for use as a treatment for novel corona virus pneumonia in clinical trials was an antiviral medication called favipiravir, which was reported to have received marketing approval for influenza treatment in China on 17 February 2020. Fujifilm announced the launch of a Phase 3 clinical trial of Avigan (favipiravir) in Japan for COVID-19 patients on March 31, 2020. Fujifilm announced the launch of a Phase 2 clinical trial of favipiravir in approximately 50 COVID-19 patients in the United States on April 9, 2020. On June 19, 2020, Glenmark Pharmaceuticals Limited announced the marketing approval in India of favipiravir (FabiFlu®) for the treatment of mild to moderate COVID-19 patients.

Fingolimod At the First Associated Hospital of Fujian Medical University in Fuzhou, China, an approved drug named fingolimod (marketed under the brand name Gilenya for the treatment of relapsing types of multiple sclerosis) is being tested as a treatment for COVID-19.

Hydroxychloroquine and azithromycin In a small study commissioned by the French government, a combination of the anti-malaria medication hydroxychloroquine and the macrolide antibacterial drug azithromycin was used to treat 20 patients with COVID-19 (Zithromax). Results showed that within 6 days of treatment, all patients taking the mixture were virologically healed.

Ivermectin In an in-vitro laboratory study by researchers at Monash University in Melbourne, Australia, an anti-parasitic drug called ivermectin has been shown to be effective against the SARS-CoV-2 virus. To confirm the efficacy of the drug in humans with COVID-19, further clinical trials need to be performed.

Leronlimab In a limited number of critically ill COVID-19 patients hospitalized in the New York area, a CCR5 antagonist named leronlimab has shown promise to calm the 'cytokine storm'.

Lopinavir and ritonavir In conjunction with the flu medication oseltamivir (Tamiflu) in Thailand, a drug combination named lopinavir/ritonavir, approved to treat HIV under the brand name Kaletra, is being tested. On February 18, 2020, it was announced that after suffering from extreme COVID-19-related pneumonia, an elderly Chinese woman, the first patient to receive the 'Thai cocktail' in Bangkok's Rajvithi Hospital, had made a full recovery. In a report published in the New England Journal of Medicine on March 18, 2020, the combination of lopinavir/ritonavir

showed no advantage over standard treatment in hospitalized adult patients with extreme COVID-19.

RLF-100 (aviptadil) is a vasoactive intestinal polypeptide (VIP) formulation that binds to lung-inhibiting pro-inflammatory cytokines from alveolar type 2 cells. Relief Therapeutics announced on August 6, 2020 that Investigational New Drug (IND) authorization had been authorized to test RLF-100 for inhaled use in patients with moderate to serious COVID-19 to avoid progression to respiratory failure.

Sarilumab As a possible therapy for acute respiratory distress syndrome (ARDS) in patients critically ill with COVID-19, an interleukin-6 (IL-6) receptor antagonist called sarilumab (marketed under the brand name Kevzara for the treatment of rheumatoid arthritis) is being tested.

STC3141 To start phase II clinical research in Australia for the treatment of acute respiratory distress syndrome (ARDS) sustained by COVID-19 patients, an investigational drug named STC3141 has been approved.

Tocilizumab An interleukin-6 receptor antagonist named tocilizumab (marketed under the Actemra brand name for the treatment of rheumatoid arthritis and other inflammatory conditions) is being tested for the treatment of patients with COVID-19 in a variety of locations worldwide **[10]**.

CONCLUSION

In conclusion, the COVID-19 pandemic is a global issue and needs unparalleled global solutions, as we will not allow people to die from complications related to the disease. Off-label use of medications has also been recommended, so that it falls under the national regulations.

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