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Anticoagulation Strategy and Recent Developments in Therapeutics for Covid 19

Bhargavan PV[1], Shiji PV[2], Blessy Josephine PB[1], Robin George[1]

[1]Department of Medicine, Baby Memorial Hospital, Kozhikode, Kerala, India
[2]Department of Medicine, Govt. Medical College, Kozhikode, Kerala, India

Address for Correspondence: Dr. Shiji PV, MD, Associate Professor, Department of Medicine, Govt. Medical College, Kozhikode, Kerala, India. Email: shijipv77@gmail.com

Abstract:

In December 2019, an outbreak of a new type of coronavirus was reported in Wuhan, China by a novel member of coronavirus genera which was officially named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) by the international committee for taxonomy of viruses based on phylogenetic analysis. It was believed to be a spill over of an animal coronavirus and later adapted ability of human to human transmission through mutation. The world health organization (WHO) termed the new virus 2019 novel coronavirus on 12 January 2020 and then officially named this disease as Coronavirus disease 2019 (Covid -19) on 12th January 2020. Severe acute respiratory syndrome Corona Virus-2 induced infection can be associated with coagulopathy and infection induced inflammatory changes in various internal organs with some features of disseminated intravascular coagulopathy. To reduce the viral load in the upper respiratory tract, repurposed antiviral drugs like Favipiravir and Remdesivir were tried initially and new molecules like Molnupiravir and Paxlovid have completed phase I trial and is found to be effective if given in the early part of the illness. Similarly, monocolonal antibodies like Bamlanivimab plus Etesevimab, Casirivimab and Imdevimab, Sotrovimab were also being given to block the entry of the virus into the respiratory epithelium and prevent the attachment of the virus to ACE II receptor leading to Covid 19 thrombo inflammation especially in older population (age > 60years) with comorbidities. Along with immunomodulator and immunosuppressant therapy, most important therapeutic intervention is early D-Dimer driven anticoagulation to prevent micro thrombi especially in the pulmonary and systemic circulation. As these modalaties of treatment are being practised in many parts of the world, it is worthwhile to review the present treatment protocol for Covid 19 infection as per the literature available at present.

Keywords: Covid 19 infection, anticoagulation, newer antivirals

Introduction

As per WHO report dated 16-11-2021, 253,640,693 confirmed cases of Covid 19 were reported so far. Till now confirmed deaths due to Covid 19 were estimated to be about 5,104,899. Vaccine doses administrated throughout the world till that date were 730,789,664. After the origin of Covid 19 (SARS-COV-2) in the last week of December 2019 in China, Covid infection has made serious health related problems with millions of people at risk in every part of the world. Thrombotic complications are a major cause of morbidity and mortality in patients with Covid 19. Patients with preexisting cardiovascular disease, multiple risk factors for

atherosclerotic vascular disease including, obesity, hypertension, diabetes mellitus, and advanced age are at the highest risk of death from Covid 19.

Attempts are ongoing for clinical trials of several known antiviral drugs, vaccines, immunomodulating, immunosuppressive agents, and antithrombotic therapy.

This review is attempting to analyze the available treatment protocol for Covid 19 which will include newer antiviral agents, and monoclonal antibodies ,antithrombotic treatment. We have assessed recent literature data on this topic and made a summary of current developments and future perspectives.

New antiviral drugs in Covid 19 infection

1. Molnupiravir

It is an experimental antiviral drug originally developed by the pharmaceutical company Merck for the treatment of influenza. Molnupiravir acts by introducing mutation into the viral genome during viral replication. A metabolite of the drug is picked up by a viral enzyme called RNA-dependent RNA polymerase and incorporated in to the viral genome resulting in nonsurvival of the virus. A word of caution is that Molnupiravir could cause mutations in human DNA as well, as per same laboratory experiments. Pregnancy could be a contraindication. This prevents the virus from spreading in our bodies and can help treating patient at risk for mild to moderate disease due to Covid 19 [1]. The phase 3 trials interim analysis showed that Molnupiravir reduced hospitalization and death by about 50% compared to placebo. If authorized Molnupiravir has the potential to become one of the first antiviral drug for Covid that can be given orally, compared to Remdesivir which needs to be given by intravenous injection over multiple days, which is approved by US FDA for treatment of Covid 19.

After the announcement by Merck on October 1st that it will be persuing Emergency Use Authorization from the US Food and Drug Administration, Britain drug regulator MHRA started recommending Molnupiravir for use in adults with mild to moderate Covid 19 and at least one risk factor for developing severe illness such as obesity, old age (above 60 years) diabetes or heart disease.

The oral drug can be taken at home as soon as possible following a positive Covid 19 test and within 5 days of onset of symptoms.

2. Paxlovid

Another drug Paxlovid by PFIZER (PE-07321333 Ritonavir) was found to reduce the risk of hospitalization or death by 89% compared to placebo in non-hospitalized high risk adults with Covid 19. In the overall study population through day 21, no deaths were reported in patients who received Paxlovid as compared to 10 deaths in patient who received placebo [2]. This drug is a combination of antiviral and another drug called Rritonavir which is used in the treatment of HIV infection and helps to prevent enzymes in the liver from breaking down the antiviral drug before it has a chance to disable the coronavirus. Ritonavir can affect the metabolism of some other cardiac medications like anti platelet agents, anticoagulants, lipid lowering drugs, calcium channel blockers and, angiotensin II receptor blockers in patients with preexisting cardiovascular disease, hypertension, diabetes mellitus, acute cardiac injury or acute coronary syndrome due to Covid 19 infection. Ritonavir is an irreversible inhibitor of CYP3A4 leading to drug-drug interaction. Protease inhibitor use was associated with increased platelet reactivity and high rate of on treatment platelet reactivity. Large clinical trials are required to establish the efficacy of this drug.

Pfizer plans to submit the data as part of its ongoing rolling submission to the US FDA for Emergency Use Authorization (EUA) as soon as possible. If approved or authorized, Paxlovid which originated in Pfizer laboratories would be another oral drug, a specifically designed SARS-COV-2-3CL protease inhibitor. The phase 2/3 EPIC-HR study began enrollment in July 2021. The phase 2/3 EPIC-SR (Evaluation of protease inhibition for Covid 19 in standard risk patients) and EPIC-PEP (Evaluation of protease inhibition for Covid

19 in post exposure prophylaxis) studies which began in august and September 2021 respectively were not included in this interim analysis and are ongoing [3].

Monoclonal antibodies

Monoclonal antibodies specific to a viral protein are alternate treatment options for viral disease. During the last decade, several targeted monoclonal antibodies were developed for the SARS-Cov spike protein to inhibit the viral fusion inside the host cell [4].

The SARS Cov-2 genome encodes 4 major structural proteins spike (s), envelope (E), membranes (M) and Nucleocapsid (N) as well as non structural and accessory proteins. The spike protein is further divided into S1 and S2 that mediate the host cell attachment and invasion. Through its receptor binding domain (RBD), S1 attaches to ACE 2 receptor on the host cell and this initiates conformational change in S2 that results in virus-host cell membrane fusion and viral entry [5].

Anti SARS Cov-2 monoclonal antibodies that target the spike protein have been shown to have a clinical benefit in treating Covid infection [6].

Three anti-SARS-Cov-2 monoclonal antibody products have emergency use authorization from the Food and Drug administration for the treatment of mild to moderate Covid 19 non hospitalized patients with laboratory confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization. These products are:

1. Bamlanivimab plus etesevimab
2. Casirivimab and indevimab
3. Sotrovimab 500 mg intravenous injection

The Covid 19 treatment guidelines panel recommends using one of the following anti SARS Cov-2 monoclonal antibodies listed in the alphabetical order to treat non hospitalised patient with mild to moderate Covid who are at high risk of clinical progression.

Casirivimab plus imdevimab dosage schedule

The panel recommends Casirivimab 600 mg plus Imdevimab 600 mg IV infusion. If IV infusions is not possible or would cause a delay in treatment, Casirivimab 600 mg plus Imdevimab 600 mg administered by four subcutaneous injections (2.5 ml) per injection can be used as an alternative.

Precautions:

1. When using monoclonal antibodies, treatment should be started as soon as possible after a patient receives a positive result on a SARS Cov-2 antigen or Nucleic Acid Amplification Test (NAAT) and within 10 days of symptoms onset.

2. The use of anti-SARS-Cov-2 monoclonal antibodies are not currently authorized for use in inpatients who are hospitalized with severe Covid 19 infection or in those who require oxygen therapy due to Covid 19.

3. Monoclonal antibodies such as Casirivimab and Imdevimab may be associated with worse clinical outcomes when administered to hospitalized patients with Covid 19 requiring high flow oxygen or mechanical ventilation.

On June 3, 2021 FDA updated the EUA for Casirivimab and Imdevimab [7]. The authorized dosages were reduced from a single infusion of Casirivimab 1200 mg plus Imdevimab 600 mg was based on the phase 3 results from the R10933-10987-Cov-2067 study (Clinical Trials.gov identifier - NCT04425629). This study

is a double-blind placebo controlled randomized trial in outpatients with mild to moderate Covid 19. The primary outcome of Covid 19 related hospitalization or death from any cause was reported in 7 of 736 patients (1.0%) with Casirivimab 600 mg/plus Imdevimab 600 mg IV arm and in 24 of 748 participants (3.2%) in the placebo arm (P< 0.0024) demonstrating a 2.21% absolute risk reduction and 70% relative reduction in hospitalization or death among the Casirivimab plus imdevimab recipients compared to the placebo recipients.

Anticoagulation in covid-19 infection

Anticoagulation therapy could represent a therapeutic barrier to corona virus complications especially pulmonary artery micro thrombosis which may be the principal cause of persistent hypoxemic status despite high flow oxygen or invasive ventilation [8].

Treatment with Heparin may be helpful in preventing this pulmonary coagulopathy as well as venous thromboembolism. A recent meta - analysis showed that adjunctive treatment with LMWH within the initial 7 days onset of ARDS reduces the risk of 7 day mortality by 48% and the risk of 28 day mortality by 37% [9].

Venous thromboembolism is one of the major cardiovascular hazards observed in 20% of critically ill COVID-19 patients which is 3-4 fold higher than the critically ill viral pneumonia patients [10].

Autopsy studies had shown that nearly 88% had a widespread thromboembolic disease [11] and small arteries (<1mm) had fibrin thrombi in 87% [12].

How to assess VTE risk apart from clinical features

Numerous scoring systems are available for the assessment of VTE risk. One of them is PADUA score. Similarly, bleeding risk (HAS - BLED) score and scoring for DIC risk (ISTH - DIC) score are recommended for sick patients admitted to ICU.

Risk Scoring systems suggested to guide anticoagulation in COVID – 19

PADUA Score		**HAS-BLED Score**		**ISTH-DIC Score**	
Active Cancer	3	Hypertension	1	Platelet Count > 100 K/dl	0
Previous Deep VTE	3	Renal Disease	1	Platelet Count 50-100 K / dl	1
Reduced mobility	3	Liver Disease	1	Platelet count < 50 K / dl	2
Known thrombophilia	3	Stroke History	1	Normal FDP levels	0
Surgery/Trauma < 1 month	2	Bleeding predisposition (or) prior Major Bleed	1	Elevated FDP levels Moderate	2
Age > 70 years	1	Labile INR	1	Prolonged PT: 3-6 seconds	1
Heart+/- lungs failure	1	Age > 65	1	Prolonged PT: > 6 second	2
Acute MI +/- AI stroke	1	Medication predisposing to bleed	1	Fibrinogen Level < 1 mg/L	0
Acute Infection / Rh disease	1	Alcohol	1	Fibrinogen Level < 1 gm/L	1
Obesity	1				
Current Hormonal treatment	1				
High Risk for VTE: Score ≥ 4		**High Risk for Bleed: Score ≥ 3**		**Overt DIC: ISTH DIC Score ≥ 5**	

Anticoagulants used in Covid-19 patients

Dose of parenteral anticoagulation during COVID-19

Dose	LMWH [Enoxaparin]	Unfractionated Heparin
Prophylactic	40 mg once a day	5000 IU subcutaneous bid
Intermediate	60 mg once a day 40 mg twice a day 0.5 mg/Kg twice a day	5000 IU subcutaneous tid or as IV infusion [target aPTT 50 -70 sec]
Therapeutic	60 mg/Kg twice a day or 1 mg/Kg twice a day	IV infusion [target aPTT 70-110 sec]

LMWH is often preferred for use in COVID-19 due to its improved pharmacodynamic, pharmacokinetic properties, predictable anticoagulant response, more favorable side effect profile, and lack of need for monitoring anticoagulant activity [13,14. Unfractionated heparin needs frequent aPTT monitoring for dose titration and also has complications like heparin-induced skin necrosis and thrombocytopenia.

Oral anticoagulants

This includes Vitamin K antagonists (VKA) and directly acting oral anticoagulants (DOACS). Compared to VKA and Heparin, DOACS have equal antithrombotic efficacy, safety profiles and can be used for therapeutic and prevention indications without any need for monitoring. DOACS are preferred for both outpatient prophylaxis and extended post-discharge prophylaxis as well as for home therapy for COVID-19 patients [15].

DOACS have a significant drug interaction with drugs like Ritonavir, Lopinavir, Azithromycin, Dexamethasone, etc after administration in COVID-19 patients.

DOACS have a longer half-life than UFH or LMWH, which is a disadvantage when urgent invasive procedures are required.

DOACS in Covid-19

Dose	Apixaban	Rivaroxaban
Prophylactic	2.5 mg twice a day	10 mg once a day
Therapeutic	5 mg twice a Day	20 mg once a day

Contraindication for anticoagulant therapy

1. Patients with active bleed or recent blood

2. Patients with platelet count < 25,000/microlitre

3. Therapeutic dose of DOAC (Apixaban) is reduced to 2.5 mg BD if the patient has two of the three risk factors (age > 80 years, body weight < 60 kg or serum creatinine level > 1.5 mg %) [16].

Management Strategy In Covid 19 Patients with coagulopathy

All admitted patients should have baseline PT, aPTT, fibrinogen, D-dimer and platelet count.

In an outpatient setting, standard VTE prophylaxis must be considered in Covid 19 infected patients with morbid obesity or past history of VTE or infected immobile patients. Routine use in outpatients is not recommended.

In inpatients admitted to the ward standard dose VTE prophylaxis can be considered after performing coagulation work up.

In ICU setting escalated dose of anticoagulants for VTE prophylaxis is considered, though there is no published data till date.

Both in confirmed VTE and presumed pulmonary embolism, therapeutic dose of anticoagulation must be considered. In ARDS, escalated dose VTE prophylaxis can be considered.

Conclusion

Nearly 23 months after the origin of Covid 19 (SARS -COV-2) in the Wuhan city of China, the total number of reported deaths have crossed 5 million on 16/11/2021. Each week more than 50,000 people are continuing to die due to Covid 19. The speed at which the virus killed people has decreased a bit since summer, this year despite the Delta variant still being the dominant strain globally. This shows that vaccination was effective in preventing deaths globally. According to WHO report, the Covid 19 pandemic is far from over as there is a rising trend in the reported cases and deaths from Covid 19 in the last 2 months. Hence it is crucial to increase the speed of vaccination especially in low income countries like Africa and Latin America, where only 1.3 % of people have received Covid 19 vaccination so far. Hence continuing research is a must for the development of new antiviral agents, immunotherapy and other vaccine like DNA vaccine to protect the human race from the hazards of this pandemic.

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