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REVIEW ARTICLE

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The use of direct acting oral anticoagulants in patients with COVID-19 infection

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ABSTRACT

The use of direct-acting oral anticoagulants (DOACs) has increased rapidly in the last decade; becoming the mainstay for both the prophylaxis and the treatment of venous thromboembolism in various situations including non-valvular atrial fibrillation, joint replacement surgeries and acute DVT/PE, etc. In the present times, DOACs are possibly one of the most widely prescribed medications in the developed world. The worldwide epidemic caused by COVID-19 caused significant changes in the practice of medicine worldwide. Patients who developed severe respiratory illness caused by COVID-19 were noted to develop a wide range of complications, including both arterial and venous thromboembolic complications including deep vein thrombosis and pulmonary embolism, etc. This review is an attempt to identify the role of DOACs in the treatment and prevention of these complications as well as the safety of continuing therapy with DOACs in the patients who were receiving them before contracting the infection.

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1. Review

The 2019 Novel coronavirus infection (COVID 19) caused by SARS COV-2 was declared a worldwide epidemic by the WHO on 11 March 2020 [1], disrupting healthcare systems worldwide with 20% of cases being severe or critical [2]. Worldwide more than 57 million people were infected by November 2020, with an average mortality rate of 2.3% according to the World Health Organization (WHO) statistics [3]. The data collected from multiple centers worldwide has shown a high incidence of thromboembolic complications in patients with COVID 19 infection. In a cohort study done by Helms et al., 64 out of 150 patients who developed ARDS secondary to COVID-19 infection and were admitted to ICU developed thromboembolic complications, including pulmonary embolisms and ischemic strokes as well as circuit clotting during renal replacement therapy [4]. The study also compared the incidence of PEs in patients with ARDS associated with severe COVID19 to that of Patients with ARDS due to other etiologies, which showed a higher rate of 11.7% in COVID-19 associated ARDS patients compared to 2.1% in non-COVID19 ARDS patients [4].

The mechanism of thromboembolic complications in critically ill patients with COVID 19 is not fully understood. Initial data from Wuhan revealed coagulopathy-related complications in 50% of patients who died of COVID 19 [5]. Multiple mechanisms of thromboembolic complications have been suggested. Besides the usual risk factors for venous thromboembolism in critically ill patients and prolonged hospitalization other mechanisms are postulated to explain increased thromboembolism in relation to COVID19 which includes widespread endothelial injury, causing intrinsic coagulation pathway activation and a flood of microthrombi and microemboli [6]. SARS COV2 virus gains entry to cells through binding to angiotensin-converting enzyme 2 (ACE2) receptors, which are widely available at the walls of endothelial cells [7]causing endothelial wall inflammation, endothelial cell injury and exposing membrane phospholipids to various plasma proteins and thus activating the coagulation cascade [6].

In the same study, done by Helms et al., lupus anticoagulants were detected in 87.7% of COVID-19 patients that were tested [4]. Though unclear at this point, mechanisms of hypercoagulability similar to antiphospholipid syndrome (APS) might have a role to play in thrombosis in COVID-19 patients [8]. Lately, there has been a debate if DOAC therapy is appropriate in patients with APS as there are published reports of patients with APS who were being treated with a DOAC were found to have recurrent thromboembolic manifestations and had to be

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switched to Vitamin K antagonists (VKAs) [9]. This could indicate that the use of DOACs in COVID 19 may not be effective in the prevention of thrombosis in this patient population as there might be a possible role of lupus anticoagulant positivity in hypercoagulation in patients with COVID19.

Moreover, DOACs are partially metabolized through the Cytochrome P450 pathway and P-glycoprotein Pathway making them a target for multiple drug interactions. As healthcare systems in different countries experimented with multiple antiviral medications during the current pandemic, the safety and efficacy of DOACs come into question [10]. In a study done by Testa et al., the plasma levels of DOACs were measured in patients hospitalized with COVID 19 who were being treated with antiviral medications such as lopinavir/ritonavir and darunavir; they found a significant increase in DOACs plasma levels [11]. The multiple drug–drug interactions, in addition to metabolic alterations that are induced by the critical illness, can result in an unpredictable and unstable DOAC effect, putting patients at risk for uncontrolled bleeding or thrombotic complications [12]. Despite the recent FDA approval of two DOACs reversal agents namely idarucizumab (a monoclonal antibody) for the reversal of dabigatran and andexanet alfa (a recombinant factor Xa) for the reversal of apixaban and rivaroxaban [13] the lack of wide availability and the high cost of these agents render their use impractical in the setting of a global pandemic.

Based on the limited data that is currently available and the inability to check the plasma levels of DOACsin the routine clinical setting, it is advised to switch patients to intravenous unfractionated Heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) especially during the treatment with antiviral medications with potential drug interactions [14]. Moreover, Chen et al. looked at the coagulation studies of 99 patients with COVID19 and found abnormal levels of D-dimer, decreased prothrombin time (PT) and increased activated partial thromboplastin time (aPTT) [15]. In another study by Tang et al. 71.4% of patients who died of COVID 19 had DIC [16]. The wide derangement of the coagulation system and homeostasis caused by novel coronavirus infection renders the effect of DOACs unpredictable, which makes LMWH or unfractionated Heparin a safer choice for easier reversibility and predictability [16]. Many hospitals and healthcare systems have put together treatment protocols for patients with severe illness due to COVID 19 for the prevention of thromboembolic complications which included switching patients from a DOAC to full anticoagulation dose with LMWH or unfractionated Heparin on admission, and to use intermediate to full dose anticoagulation for high-risk patients with significantly elevated D-dimer levels [17]. At the same time guidelines by the National Institute of Health (NIH), recommend continuation of anticoagulant regimen that patient is already receiving and also emphasized consideration of extended prophylactic anticoagulation for upto 6 weeks in certain high-risk patients after discharge [18]. As the knowledge in the field of COVID19 and coagulation abnormalities is still evolving there is no solid consensus among the medical community in relation to management of these patients but with ongoing research more evidence is expected to emerge and will provide more insight on this subject.

2. Conclusion

In light of the limited available data, it would be safer to recommend switching COVID 19 patients from DOACs to LMWH or UFH for the duration of acute illness for which they are expected to receive medications that can interact with DOACs, or are expected to have coagulation system and homeostasis derangements. Also, extended prophylactic anticoagulation after discharge from the hospital is recommended in certain high-risk patients on case by case basis. It might be worth noting that the use of a DOAC may be a more practical option than LMWH after discharge for some patients with milder cases of COVID 19 who are on a steady track for recovery, mainly patients who are showing improvement in their inflammatory markers and D-Dimer levels and with normal coagulation profile. However, more studies are needed to assess the safety of DOACs in the post discharge phase in COVID 19 patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Timeline of WHO's response to COVID-19. 2020; Available from: https://www.who.int/news-room/detail/29-06-2020-covidtimeline.
[2] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. Jama. 2020;323 (13):1239–1242.

[3] WHO coronavirus disease (COVID-19) dashboard. 2020; Available from: https://covid19.who.int.
[4] Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089–1098. .
[5] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–1062. .
[6] Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120–128. .
[7] Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111(20):2605–2610. .
[8] Negrini S, Pappalardo F, Murdaca G, et al. The antiphospholipid syndrome: from pathophysiology to treatment. Clin Exp Med. 2017;17(3):257–267. .
[9] Joshi A, Hong J, Siva C. Recurrent thrombosis in patients with antiphospholipid syndrome receiving newer oral anticoagulants: a case report and review of literature. Clin Med Res. 2017;15(1–2):41–44.
[10] Foerster KI, Hermann S, Mikus G, et al. Drug-drug interactions with direct oral anticoagulants. Clin Pharmacokinet. 2020;59(8):967–980. .
[11] Testa S, Prandoni P, Paoletti O, et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: the Cremona experience. J Thromb Haemost. 2020;18(6):1320–1323. .
[12] Testa S, Legnani C, Antonucci E, et al. Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants. J Thromb Haemost. 2019;17(7):1064–1072. .
[13] Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the Anticoagulation Forum. Am J Hematol. 2019;94(6):697–709. .
[14] Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. Chest. 2020;158(3):1143–1163. .
[15] 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(10223):507–513. .
[16] Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):p. p. 844–847. .
[17] Hematology recommendations and dosing guidelines during COVID-19. 2020. Available from: https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/guidance-from-mass-general-hematology.pdf.
[18] Antithrombotic therapy in patients with COVID-19. 2020. Available from: https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/.