DOAC in COVID-19: Yes or No?

Roger E. Schutgens

Correspondence: Roger E. Schutgens, *HemaSphere Scientific Editor* (r.schutgens@umcutrecht.nl).

It is commonly known that coronavirus disease 2019 (COVID-19) exposes patients at increased risk for thrombosis. Prevalences range from 2.6% to 35.3% from earlier reports and despite adequate thromboprophylaxis symptomatic venous thromboembolism (VTE) occurs in 4.4% of patients, ischemic stroke in 2.5%, and myocardial infarction in 1.1%.[1] Available evidence suggests that the coagulopathy associated with COVID-19 is a combination of low-grade disseminated intravascular coagulation (DIC) and localized pulmonary thrombotic microangiopathy.[2] Current guidelines recommend thromboprophylaxis with low-molecular-weight heparin (LMWH) in all hospitalized COVID-19 patients. The American College of Chest Physicians suggests prophylactic dose LMWH in all patients, while the International Society on Thrombosis and Hemostasis also suggests half-therapeutic dose in patients at high risk.[1]

Direct oral anticoagulant (DOAC) drugs are now standard of treatment in venous thrombosis and atrial fibrillation. Therefore, the chance of hospital admission for patients already treated with a DOAC is increasing. Even more so, treatment of COVID-19 related pulmonary embolism with a DOAC is done in many clinics. But what is the current evidence of their use in COVID-19?

DOAC and cytochrome P450

DOACs interact with P-glycoprotein and/or cytochrome P450 (CYP)-based metabolic pathways. Many classes of drugs cause drug-drug interactions, in such a way modifying the DOAC pharmacodynamic and pharmacokinetic profile and causing a remarkable decrease or increase of their anticoagulant action. Indeed, antiviral drugs such as remdesivir are substrates of CYP 3A4, CYP 2D6, and CYP 2C8. Dexamethasone is also an inducer of CYP3A4. The multiple drug-drug interactions (antiviral, antibiotics, antihypertensive, bronchodilators, and immunosuppressive drugs), in addition to metabolic alterations that are induced by the acute disease, can cause an unpredictable and unstable DOAC anticoagulant effect, exposing patients to the risk of uncontrolled bleeding or thrombotic complications.[3] In addition, acute kidney injury in patients hospitalized for COVID-19 infection is frequent, with an incidence of about 3%–15% that increases up to 50% in most severe patients such as those admitted in intensive care units.[4]

Antiviral therapy

An Italian report analyzed 1039 patients hospitalized COVID-19 pneumonia and candidates for antiviral therapy, of whom 32 were on treatment with a DOAC.[5] In 12 patients, the DOAC was continued during treatment with antiviral drugs. For each patient, C-trough DOAC level was compared with the one measured at a thrombosis center before hospitalization, where a structured follow-up is applied. In all 12 examined patients, an alarming increase in DOAC plasma levels compared with prehospitalization was observed after hospital admission (Figure 1).
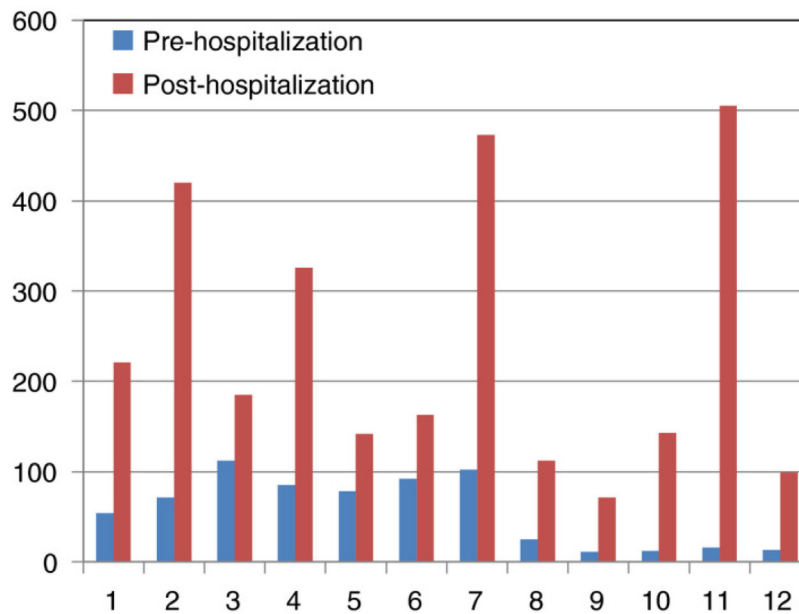
Disease-drug interaction

The immune response, with interleukin (IL)-6 in the core of its network of mediators, is a hallmark of COVID-19 pathogenesis.[6] This implicates that COVID-19 itself will have an impact on the CYP regulation. In the latter review, it is strongly postulated that CYPs metabolic activity will be inevitably altered, mostly down-regulated, during the course of severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2), resulting in a clearance-related pharmacokinetic interaction with the administered drugs.

Blocking the IL-6 receptor (tocilizumab or sarilumab) is therefore focus of research. Current published reports show mixed effects of tocilizumab on the outcome in COVID-19. Very recently,

Figure 1. Changes in C-trough levels (ng/mL) of DOAC in 12 patients with COVID-19. Figure from Testa et al.[5] COVID-19 = coronavirus disease 2019; DOAC = direct oral anticoagulant.

the REMAP CAP platform reported encouraging results on mortality on 2000 patients,[7] which might lead to more use of tocilizumab in severe COVID-19 patients in the near future. The same is true for IL-1 blockade (anakinra).

DOAC: stop or start?

There are currently no clinical data on safety or efficacy of DOAC use in COVID-19 patients. There is one retrospective cohort study that acted as a simulation intention-to-treat trial on the effect of anticoagulation therapy chosen in the first 48 hours of hospitalization in 3625 inpatients.[8] A significant decrease in mortality with prophylactic use of apixaban (odds ratio [OR] = 0.46, $P = 0.001$) and enoxaparin (OR = 0.49, $P = 0.001$) was seen. Therapeutic apixaban was also associated with decreased mortality (OR = 0.57, $P = 0.006$) but was not more beneficial than prophylactic use when analyzed over the entire cohort or within D-dimer stratified categories.

Patients admitted with COVID-19 using DOAC at home

In light of the above, DOACs should theoretically be stopped and switched to an alternative anticoagulation drug in patients admitted with COVID-19 who are candidates for antiviral or anti-IL6/IL1 therapy. The same goes for the concomitant use of dexamethasone. As the effect of dexamethasone on the CYP system lasts for a week, DOACs might be restarted again after discharge with a minimum of 1 week after stopping dexamethasone. As the risk of interactions between drugs differs with the type of DOAC, it seems that dabigatran may be the DOAC with the lowest risk of interactions with COVID-19 drugs that are metabolized via cytochrome P450.[9]

Patients admitted with COVID-19 who develop thrombosis during admission

Whether newly diagnosed venous thrombosis during COVID-19 should be treated with a DOAC or not is unknown. Recently, the ISTH DIC subcommittee published a communication on

anticoagulation in COVID[10]: there was no mentioning of the use of DOACs. In fact, a comparison of 7 recently published guidelines on this topic indicates that nowhere DOAC is considered to be a preferable option.[11] In patients treated with dexamethasone, antiviral therapy or anti-IL6/1, it is therefore sensible to use LMWH or UFH, which can be switched to a DOAC later on.

Conclusion

The use of DOACs in hospitalized COVID-19 patients is not straightforward. There is ample evidence that both COVID-19 disease and its related treatments have an impact on the cytochrome P450 pathways. This, in turn, might cause decreased or increased anticoagulation activity. As alternative methods (including LMWH) are widely available, it seems wise at this point to stop, convert, or not start DOACs in these patients until more clinical data support their use.

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