

Impact of the COVID-19 pandemic on therapeutic choices in thrombosis-hemostasis

Major therapeutic developments have been achieved in the field of thrombotic and hemorrhagic diseases over the last decade. These include the development and validation of four direct oral anticoagulants (DOACs) indicated for numerous thrombotic disorders, both arterial and venous.¹ Developments also involve new hemostatic agents for hemophilia patients, in particular factor VIII (FVIII) and factor IX (FIX) concentrates with extended half-life (EHL)^{2,3} and a bispecific antibody mimicking the action of FVIII (emicizumab).^{4,5}

No one can dispute the major benefits of these widely adopted drugs, which have fundamentally changed the management of many patients. Among the benefits of DOACs are their antithrombotic efficacy equal to or superior to anticoagulation with vitamin K antagonists (VKAs) or heparins, and their safety and ease of use in many therapeutic or preventive indications.⁶⁻⁸

At the same time, EHL-FVIII and especially EHL-FIX concentrates offer significant advantages over standard half-life FVIII and FIX concentrates. The benefits are even greater for emicizumab. This agent makes it possible to treat hemophilia A patients with and without inhibitors with infrequent subcutaneous injections (1x/week to 1x/4 weeks) while maintaining steady coagulant activity.

The benefits of these various drugs are well recognized by health-care professionals. These benefits appear even greater in the context of the COVID-19 pandemic and health crisis that is sweeping the planet and the containment it requires for hundreds of millions of people.

The current situation imposes restrictions on mobility; reduces access to medical care, both general practitioners and hospitals; and access to pharmacies, laboratories, and nursing care. As for hospitals, many are saturated and devote most of their resources to the management of patients with COVID-19. In this context, the benefits of DOACs and new treatments for hemophilia appear even more obvious.

For DOACs, the administration of a fixed dose, the absence of monitoring, the limited number of drug interferences, the monotherapy without prior treatment with heparins for patients with acute venous thromboembolic disease, and the absence of bridging with heparin during invasive procedures are all major advantages. Added to this is the reduction of the risk of

hemorrhage with DOACs, which is relevant as access to emergency rooms is becoming problematic and blood products must be spared.

On this basis, the current crisis offers multiple arguments for favoring anticoagulation with DOACs in patients without contra-indications. For patients in whom oral anticoagulation must be started, it seems legitimate to favor the use of DOACs. For patients on long-term VKA, the current crisis is probably an opportunity to switch them to a DOAC. For patients who should imperatively be or remain on VKAs (mechanical cardiac valve, antiphospholipid syndrome, renal impairment depending on its severity, and so on), the use of point-of-care (POC) devices for measuring international normalized ratio (INR) should be promoted. However, it will be difficult to implement such monitoring in the midst of the crisis due to the potentially limited availability of POC devices, strips, and logistical barriers of education. It seems clear, however, that greater use of INR measurements by POC devices in the future should prevent and avoid monitoring difficulties in the event of a new health crisis.

For hemophilia patients who are candidates for prophylactic treatment, EHL-FVIII and especially EHL-FIX concentrates represent a valuable alternative. The benefits are multiple: limitation of the number of injections, better protection against bleeding episodes, less frequency of supply.

For emicizumab, too, the benefits are numerous: avoidance of intravenous injections, which is important for patients unable to perform self-infusions; infrequent subcutaneous injections; stable effect providing very good and prolonged protection against bleeding episodes, including patients with inhibitors against FVIII.

Any critical situation amplifies well-known daily difficulties that are often minimized and for which existing solutions are frequently insufficiently implemented. DOACs and new hemostatic treatments offer major advantages that are even more obvious in times of crisis. The current pandemic highlights many arguments in favor of these drugs and is expected to have a significant impact on their use in the short and long term.

KEYWORDS


clotting factor concentrates, COVID-19, direct oral anticoagulants, emicizumab, hemophilia, pandemic

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Both authors contributed to the writing of this manuscript.

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DOACs and “newer” hemophilia therapies in COVID-19: Reply

We thank the authors for their insightful thoughts on the consideration of anticoagulants and treatment for hemophilia A and B during the COVID-19 pandemic. They highlight some important practical points that certainly should be adopted by the thrombosis and hemostasis community in the current situation of restricted mobility, which reduces the possibility for patients to access general practitioners and hospitals. In relation to the use of direct oral anticoagulants (DOACs), the authors suggest to consider the current crisis as an opportunity to switch patients receiving vitamin K antagonists (VKA) to a DOAC as long as it is within the indication (excluding patients with mechanical heart valves or antiphospholipid syndrome). In addition, we think this may be an opportunity to consider DOACs for indications such as unusual-site thromboses like cerebral venous thrombosis and noncirrhotic portal vein thrombosis, where DOACs have been trialed but not yet been accepted for widespread use.^{1,2} Another area, where this is similarly relevant is patients who have an underlying malignancy who may be receiving chemotherapy or

their treatment may have been withheld due to the pandemic from concerns of immunosuppression. Although, low molecular weight heparin is the drug of choice in patients with cancer, recent trials have clearly shown equal efficacy for DOACs and low molecular weight heparin in these patients and appropriate patients (except those with gastrointestinal and genitourinary cancers) may be considered for DOACs treatment of cancer-associated thrombosis.³⁻⁶ DOAC are certainly of more practical use than VKA especially during COVID-19 pandemic because they do not need laboratory monitoring. In addition, they proved safer than VKA in terms of incidence of intracranial bleeding, although it must be emphasized, contrary to what Hermans and Lambert implied in their letter, that they did not prove safer than VKA in terms of incidence of bleeding in other sites (especially gastrointestinal), which may be severe enough to require transfusion of blood products. We do, however, advise *caution* (not avoidance) with DOACs in patients admitted with COVID-19 illness (who can continue to take oral medications) for the following reasons

- Interactions with antiretroviral drugs should be taken into account since some of these drugs have been considered in the treatment