Commentary

Light and shadows of the new therapies for haemophilia treatment in the COVID-19 era

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Coronavirus disease (COVID-19) is an infectious disease caused by a novel coronavirus (SARS-CoV-2). The onset symptoms are similar to those of seasonal flu, but can easily develop into severe respiratory failure with the need for hospitalisation. In addition to these respiratory outcomes, some changes in coagulation parameters have been observed, especially in those patients more severely affected, who are therefore associated with a poor prognosis, as reported by Arachchillage and Laffan[1]. D-dimer, activated partial thromboplastin time (aPTT) and prothrombin time (PT) were increased in almost all patients, as reported by Tang *et al.*[2] and Terpos *et al.*[3] Disseminated intravascular coagulation (DIC) was considered as a predictor of mortality in patients with COVID-19[2,4], while venous thromboembolism is considered an emerging issue due to patients' characteristics: often elderly with severe comorbidities and long-term immobilisation[3].

To date, only one case of a haemophilia patient presenting mild SARS-CoV-2 infection has been published[5], therefore it is not yet clear what the role of coagulation changes may be in patients with hereditary bleeding disorders. Our recent experience in a mild haemophilia A patient presenting FVIII of 25% at diagnosis and vWF:Ag of 82.7% infected by SARS-CoV-2 showed an increase in these parameters, reaching a peak of 140.5% and 638.7%, respectively. The D-dimer was also significantly increased 15 days after hospitalisation (4,075 µg/dL), while both fibrinogen and antithrombin always remained in the normal range. The rise in some of these parameters has already been described by many other authors in patients without underlying coagulation disorders[6,7], while only few data on the increase in FVIII are reported by Panigada *et al.*[8] in their recent report on 24 COVID-19 non-haemophilia patients hospitalised in an intensive care unit and evaluated by thromboelastography.

Hermans and Lambert[9] highlighted the benefits of the new therapies for the treatment of patients with haemophilia during the COVID-19 pandemic. These include the extended half-life (EHL) coagulation factor concentrates, that can be administered to patients with longer intervals between infusions, or the new subcutaneous drugs, such as emicizumab, which greatly reduce hospital admissions at a time when healthcare systems are facing a challenging and unexpected emergency.

In addition to the benefits provided by these new drugs, however, it is important to consider the problems which can arise in the case of COVID-19 patients. Special consideration should be given to those patients on prophylactic treatment with emicizumab and those currently enrolled on some experimental clinical trials for the use of the subcutaneous drugs fitusiran and concizumab. In fact, the recent recommendations of the World

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Federation of Hemophilia (WFH) also suggest the need for careful attention to the treatment of patients with haemophilia for the correct management of COVID-19[10].

EMICIZUMAB

Emicizumab is a bispecific monoclonal antibody which mimics the action of FVIIIa by binding to factor IXa (FIXa) and factor X (FX), and promoting the activation of FX in FXa, thus restoring the normal process of blood coagulation. Emicizumab can be used as antihaemorrhagic prophylaxis in haemophilia A patients with and without inhibitors. Its plasma concentration reaches the steady state after four weeks of treatment with a loading dose and is maintained by prophylactic administration of the drug once a week, every 15 days or once a month[11]. However, emicizumab can interfere with laboratory tests. This means that if a patient on prophylactic treatment with this drug and a suspected SARS-CoV-2 infection comes to our attention, care must be taken not to misinterpret the laboratory results. Interference from emicizumab concerns in particular the aPTT and all the functional tests related to aPTT, such as one-stage factor concentration, functional activity of protein C/protein S, and resistance to activated protein C, which give clearly overestimated values of the coagulation activity and therefore cannot be used in clinical practice. A chromogenic method with bovine reagent is needed to avoid this type of interference. There is less interference with PT, while in measuring plasmatic D-dimer level, AT and anti-Xa activity are not described. Although five thromboembolic events were reported during clinical trials associated with the concomitant use of high-dose bypassing agents, and 14 events in real-life clinical practice, to date there are no reported cases of venous thromboembolism related to the use of emicizumab during SARS-CoV-2 infection.

FITUSIRAN

Fitusiran is an RNA interference (RNAi) that binds and degrades the messenger RNA (mRNA) and silences the antithrombin (AT) gene, inhibiting AT synthesis. The reduction in AT is dose-dependent, and an increased dose of fitusiran leads to an increase in thrombin generation and a consequent reduction in bleeding. Fitusiran is currently used in clinical trials as an anti-haemorrhagic prophylaxis in haemophilia A or B patients, with or without inhibitors, at a dosage of 80 mg once a month. A fatal cerebral sinus thrombosis occurred in a severe haemophilia A patient during the drug development phase in association with the concomitant use of daily high-dose FVIII concentrate[12]. Following this, the trial was initially stopped, and then later resumed indicating a very low maximum concomitant use of FVIII or FIX (10 IU/kg) concentrates to prevent the risk of thrombotic events due to the concomitant presence of a low AT (15-20%) and an elevated plasma FVIII/FIX. In addition to acting on AT, fitusiran acts on D-dimer, so much so that most patients treated with this drug reach very high values of this parameter[13]. Therefore, patients treated with fitusiran who have a SARS-CoV-2 infection must be very carefully managed as the risk of a thromboembolic event is very high. In fact, SARS-CoV-2 can cause an increase in the D-dimer level, FVIII and vWF. These changes can result in a clinically significant hypercoaguable state. Management of the COVID-19 haemophilia patient in treatment with fitusiran, therefore, is seriously problematic. In fact, the long half-life of this drug in the liver that inhibits AT formation does not allow it to be eliminated in time to reduce its pro-coagulant effect. Effective concomitant antithrombotic therapy is very important, and should be associated with the treatment of the infectious disease under constant monitoring. To reduce the thromboembolic risk, using AT as reversal of fitusiran could be considered, to be followed by the eventual establishment of a prophylactic treatment with FVIII o FIX concentrate with which to associate the antithrombotic prophylaxis. The management of haemophilia patients with inhibitors is more difficult. In fact, the suspension of fitusiran requires the use of a prophylaxis with bypassing agents, which are drugs with an elevated thromboembolic risk.

CONCIZUMAB

Concizumab is monoclonal antibody inhibiting tissue factor pathway inhibitor (TFPI). It is a high-affinity, humanised, monoclonal IgG4 antibody directed against the Kunitz-2 domain of human TFPI. Concizumb can then neutralise the TFPI inhibition of FXa/TF/FVIIa, prolong the coagulation onset phase, and restore the

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thrombin generation potential in haemophilia patients[14]. Concizumab is currently being used in clinical trials as an anti-haemorrhagic prophylaxis in haemophilia A or B patients, with or without inhibitors, at a dosage of 0.15 mg/kg daily after a first loading dose of 0.5 mg/kg. Like fitusiran, concizumab also increases the levels of D-dimer, observed during phase I/II trials[15,16], and increases levels of the fragments prothrombin F1 +2, while no other changes have been observed in the other laboratory parameters. Therefore, also in this case, we are witnessing the onset of a hypercoagulable state which, combined with that caused by the SARS-CoV-2 infection, can lead to an increase in the thromboembolic risk in haemophilia patients receiving concizumab. The patients treated with this drug should, therefore, be closely monitored to avoid the risk of severe adverse events, and an antithrombotic therapy should be considered given the increase in pro-coagulant parameters. Also in the case of concizumab, as for fitusiran, suspension of the drug could be considered in order to reduce the risk of thromboembolic events resulting from the increase of some coagulation parameters. In this case, due to the short half-life of concizumab (about 30 hours), no reversal would be necessary and a prophylaxis with FVIII or FIX could be immediately started, associated with an antithrombotic treatment. Also in this case, the problem of haemophilia patients with inhibitors remains, as the use of bypassing agents would not reduce the risk of thromboembolic events in a context such as that of COVID-19 in which a hypercoagulable state has been established.

In this context, we have attempted to identify the different possible scenarios should haemophilia patients treated with these new drugs present SARS-CoV-2 infection, compared with those treated with standard or EHL factor coagulation concentrates (**Table I**).

Table I - *Different management approaches in haemophilia patients treated with new subcutaneous drugs or coagulation factor concentrates during SARS-CoV-2 infection*

Drug	Route	D-dimer	AT	Management	Antithrombotic therapy
Concizumab	SC	Increased	No change	We suggest: • to maintain the treatment, adding antithrombotic therapy	We suggest: • prophylactic dose of LMWH/UFH (e.g. 4,000 IU/day) or fondaparinux (2.5 mg/day)
Fitusiran	SC	Heavily increased	Heavily reduced	We suggest: • to maintain the treatment, adding antithrombotic therapy • to reverse the fitusiran with AT administration, then establish a prophylaxis with SHL or EHL coagulation factor concentrates, adding at the same time an antithrombotic therapy	We suggest: • prophylactic dose of LMWH/UFH (e.g. 4,000 IU/day) or fondaparinux (2.5 mg/day); in case of prophylaxis with SHL or EHL FVIII/FIX, their plasmatic level should be ≥30%
Emicizumab	SC	No change	No change	We suggest: • to maintain the treatment, adding antithrombotic therapy	We suggest: • prophylactic dose of LMWH/UFH (e.g. 4,000 IU/day) or fondaparinux (2.5 mg/day)
SHL concentrates	IV	No change	No change	We suggest: • to maintain the treatment, adding antithrombotic therapy	We suggest: • low-dose of LMWH/UFH (e.g. 2,000 IU/day) or fondaparinux (1.5 mg/day) is FVIII/FIX 5-30% • prophylactic dose of LMWH/UFH (e.g. 4,000 IU/day) or fondaparinux (2.5 mg/day) if FVIII/FIX ≥30%
EHL concentrates	IV	No change	No change	We suggest: • to maintain the treatment, adding antithrombotic therapy	We suggest: • low-dose of LMWH/UFH (e.g. 2,000 IU/day) or fondaparinux (1.5mg/day) is FVIII/FIX 5-30% • prophylactic dose of LMWH/UFH (e.g. 4,000 IU/day) or fondaparinux (2.5 mg/day) if FVIII/FIX ≥30%

SC: subcutaneous; IV: intravenous; SHL: standard half-life; EHL: extended half-life; AT: antithrombin; FVIII: factor VIII; FIX: factor IX; LMWH: low molecular weight heparin; UFH: unfractionated heparin.

Therefore, haemophilia clinicians face a new challenge, and certainly not the last. In the future, it will be increasingly important to have a complete understanding of the characteristics of the available drugs and adopt a tailored therapy approach to use them in the most suitable way for each individual patient.

Key words: COVID-19 complications, haemophilia, emicizumab, fitusiran, concizumab.

The Authors declare no conflicts of interest.

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