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Reperfusion therapy of ischaemic strokes in oral anticoagulated patients: an expanding field in clinical practice

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To the Editors

The optimum treatment for acute ischaemic stroke in patients receiving active anticoagulation, i.e. with effective levels of anticoagulant activity, which most commonly represent the anti-Xa activity of rivaroxaban, apixaban or edoxaban administration or anti-IIa activity after the administration of dabigatran, is unresolved due to relatively poor empirical data.

This is an increasing problem in clinical practice because of the growing use of oral anticoagulants and the associated occurrences of intracranial haemorrhages (ICH) and ischaemic strokes, occurring despite the desirable anticoagulant blood concentrations achieved [1–5].

Current empirical and observational data shows that in patients with acute ischaemic stroke who receive dabigatran, the administration of idarucizumab, a monoclinal antibody that reverses anti-IIa activity, followed by recombinant tissue plasminogen activator (rtPT), is reasonably safe. However, the clinical efficacy of this treatment regimen remains unproven in terms of Evidence-Based Medicine. The low level of evidence (LOE) for clinical outcomes is the result of various factors, including a lack of randomised trials, diverse inclusion criteria in the available observational studies, and the relatively low number of patients in these studies [6–15]. Therefore, information on a new series of patients from different populations might be valuable in establishing management standards [16].

Nevertheless, at the moment, a combination of pharmaceutical and observational data has resulted in positive narrative recommendations from most European experts regarding the use of idarucizumab followed by rtPA for non-large vessel occlusion (non-LVO) stroke in patients with high anti-IIa activity or expected anti-IIa activity [17–19]; the administration of idarucizumab to a patient with no or little anti-IIa activity should not generate any major side effects or complications other than those associated with the administration of any monoclinal antibody [20].

The effectiveness of andexanet alpha, an analogue of endogenous FXa that reverses the effect of all direct and some indirect Xa factor inhibitors (e.g. unfractionated heparin, low-molecular weight heparin and fondaparinux), is more debatable than the use of idarucizumab, even considering the intracranial haemorrhage, especially in view of the recently released results of the ANNEXA-I study at the World Stroke Conference [21], even though it has real promise for some ICH patient subgroups. The use of andexanet alpha in combination with thrombolytics in acute cerebral ischaemia on anti-Xa anticoagulation has been reported in only two cases [19, 22]. The pharmacodynamics and pharmacokinetics of this agent are more complex than those of idarucizumab, it requires a different administration regime (i.e. an intravenous bolus followed by infusion), and its application in ICH patients has been associated with more prothrombotic complications, including ischaemic strokes and myocardial infarctions [21, 23].

Thus far, STROACT (STROke on AntiCoagulants for Thrombolysis), ongoing in selected Polish centres, is the only large-scale study to have evaluated the efficacy and safety of reperfusion thrombolytic therapy with intravenous rtPA for ischaemic stroke in patients receiving non-vitamin K antagonist oral anticoagulants after reversing anticoagulant activity with a specific antidote (https://www.frontiersin.org/articles/10.3389/fneur.2023.1269651/full#supplementary-material). Its 'anti-IIa' substudy is confirmatory to previous reports [7–11, 20] and aims to upgrade the level of evidence for the clinical efficiency of this therapeutic protocol, whereas the substantial 'anti-Xa' substudy tests a novel, four-step, 3-hour therapeutic protocol developed and used for the first time by ourselves [19].

However, before the time of its completion, or indeed that of any potential new study, andexanet alpha should not be administered in ischaemic stroke in any combinations with thrombolytics. This is for multiple reasons, but primarily because of its prothrombotic action that is seen both in specific

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laboratory data and in clinical observations in patients with ICH, although this complication has not been found in healthy volunteers.

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