Thrombosis Research 164 (2018) S119–S123

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Antidotes for the direct oral anticoagulants: What news?

Galliazzo S., Donadini M.P., Ageno W.*

Research Center on Thromboembolic Diseases and Antithrombotic Drugs, Department of Medicine and Surgery, University of Insubria, Varese, Italy

ARTICLE INFO

Keywords:
Antidote
Direct oral anitcoagulant
Haemorrhage
Surgery

ABSTRACT

The direct oral anticoagulants (DOACs) are recommended as the first-choice anticoagulants for both stroke prevention in patients with non-valvular atrial fibrillation and the treatment and secondary prevention of venous thromboembolism. DOACs cause bleeding, albeit less than warfarin. Most bleeding complications can be controlled by general reversal strategies and supportive care. However, in case of life-threatening bleeding, or when urgent invasive procedures are needed, a more rapid and thorough reversal may be required. Idarucizumab, andexanet alfa and ciraparantag have been developed as reversal agents for the DOACs. To date idarucizumab is the only approved antidote and is specific for dabigatran. Andexanet alfa, a reversal agent for the factor Xa inhibitors, is still under investigation, but its approval by regulatory agencies is expected soon. Ciraparantag, a universal antidote, is in an earlier stage of development. Based on the results of clinical trials to date, these compounds appear to be breakthrough for urgent and emergency reversal. When administered at fixed doses, they ensured a rapid, efficient and safe restoration of haemostasis. From a practical perspective, all hospitals should develop local protocols to ensure safe and efficient clinical implementation of reversal strategies. Post-marketing studies will be essential to assess the evolution of management strategies and to confirm the safety and effectiveness of these agents.

1. Introduction

In the last decade the armamentarium for antithrombotic therapy was enriched by the availability of the direct oral anticoagulants (DOACs). After more than 60 years in which vitamin K antagonists (VKAs) have represented the only oral anticoagulant option, four DOACs have been licensed one after the other. These agents selectively and directly target activated clotting factors, either factor IIa, such as in the case of dabigatran etexilate or factor Xa, such as in the case of rivaroxaban, apixaban and edoxaban. These compounds have addressed some of the unmet needs with the use of VKAs and are now recommended by international guidelines as the first-choice anticoagulants for both stroke prevention in patients with non-valvular atrial fibrillation (NVAF) and the treatment and secondary prevention of venous thromboembolism (VTE) [1,2].

These recommendations are based on the results of a number of phase III randomized clinical trials (RCTs), which consistently proved that the DOACs have a more favourable risk-benefit profile than warfarin, both in VTE and in NVAF patients. Of note, VTE treatment with the DOACs resulted in a 39% relative risk reduction of major bleeding and in a more than 60% reduction in fatal and intracranial haemorrhages [3]. Similarly, in NVAF patients a 52% relative risk reduction in the rate of intracranial bleeding was observed [4]. In a systematic pooled analysis of safety outcomes from 12 phase-3 RCTs, involving more than 100,000 patients with VTE or NVAF, the DOACs were associated to a reduction of 47% in fatal bleeding and of 57% in intracranial bleeding as compared with warfarin [5]. In addition, the computed case-fatality rate for major bleeding was 7.57% for DOACs and 11.05% for warfarin [6]. The clinical benefit of the DOACs was subsequently confirmed by a number of post-marketing studies [7–12].

Despite the favourable results of clinical studies, bleeding with effective anticoagulants such as the DOACs may occur and the case fatality rates remain non-negligible. For this reason, physicians have initially expressed concerns about the lack of specific reversal agents and the absence of validated protocols for the management of emergency situations. These concerns have fostered research on specific drug antidotes.

2. General management strategies of major and life-threatening bleedings

Anticoagulants are the most common culprit drug class of adverse events requiring emergency department admission, especially in elderly outpatients, as shown by data derived from an US National Surveillance Program [13,14]. Different strategies have been validated over the years for the management of bleeding complications in patients treated

* Corresponding author at: Degenza Breve Internistica e Centro Trombosi ed Emostasi, Ospedale di Circolo, Via Guicciardini 9, 21100 Varese, Italy.
E-mail address: walter.ageno@uninsubria.it (W. Ageno).

https://doi.org/10.1016/j.thromres.2018.01.006
Received 17 November 2017; Received in revised form 2 January 2018; Accepted 3 January 2018

with VKAs [15]. Despite scant available evidence, as of yet, guidance for the management of patients treated with the DOACs has been recently published [16].

Differently from VKAs, "time" is an important factor for DOACs reversal, given their rapid offset of action [17]. Thus, DOACs withdrawal is the first step for restoring haemostasis. To ensure the correct estimation of the time required for the individual patient, information on when the last dose was taken and on patient renal function should be collected. Of course, emergency situations usually require a more rapid reversal than the time needed for DOACs elimination. Hence, a number of additional measures have been proposed to rapidly restore a normal coagulation and stop bleeding. Among reversal measures, general and specific agents should be distinguished. The first encompass strategies that affect DOACs pharmacokinetics and agents that bypass their anticoagulant activity. DOACs pharmacokinetics can be speeded by decreasing their gastric absorption and/or promoting their clearance. Gastric absorption can be reduced by oral activated charcoal administration within 2 h from the last dose of apixaban or dabigatran. This strategy can be reasonably extended to all DOACs, even if specific data on rivaroxaban and edoxaban are not available. For dabigatran only, elimination can be forced through haemodialysis, thanks to its low binding to plasmatic proteins [18].

The use of bypass agents is drawn from recommendations for VKA-related major bleeding management [15,19–21]. High quality evidence about the role of prothrombin complex concentrates (PCC), activated prothrombin complex concentrates (aPCC), and recombinant active FVII (rFVII) for DOACs reversal is lacking. The only available data arise from animal models, in vitro and ex-vivo studies on healthy volunteers [22–24]. The mechanism by which these agents accomplish DOACs reversal remains unclear. Replacement of vitamin K dependent clotting factors, acting upstream the coagulation common pathway, appears a controversial strategy to bypass DOACs effect. PCC show different ability to reverse FIIa- and FXa- inhibitors activity. In a small study involving 12 healthy anticoagulated volunteers, 4-factors PCC (4F-PCC) reversed the activity of rivaroxaban, without any influence on dabigatran effect [25]. The efficacy of 4F-PCC in restoring haemostasis was also demonstrated in edoxaban-treated healthy volunteers undergoing punch biopsy [26]. Recently, PCC, aPCC and rFVII have been compared using blood collected from 50 patients on therapeutic rivaroxaban dose. Activated PCC resulted the best strategy to reverse the rivaroxaban anticoagulant effect, as assessed by thromboelastometry and thrombin generation assay. Furthermore, no difference in haemostatic effect was observed by increasing the aPCC dose from 80% to 125% of the suggested dose of 50UI/Kg endorsed by current algorithms for reversal managing [18,27]. Fresh-frozen plasma (FFP) is not included among the potential general reversal strategies as its low clotting factors concentration fails to overcome DOACs effect. Finally, very little evidence is available on rFVIIa for DAOCs reversal, but the prothrombotic effects and the costs of this agent make its use in this setting unlikely.

3. DOACs specific reversal agents

The development of specific antidotes aimed to address the criticism on the proper handling of DOACs related bleeding in the emergency setting [28]. The ideal antidote should be specific for the anticoagulant drug on board, efficient with a rapid, predictable and stable reversal anticoagulant activity, easy to administer and safe without prothrombotic effects, major adverse events and rebound anticoagulant effect [29]. The three reversal agents in the more advanced stage of development include Idarucizumab, andexanet alfa and ciraparantag. Idarucizumab has received an expedited approval by the Food and Drug Administration (FDA) in 2015 and, subsequently, by the European Medicine Association (EMA) and other national agencies worldwide. Andexanet alfa and ciraparantag are still under investigation and their development program is supported by the breakthrough therapy and fast-track designation granted by FDA, respectively [30]. The approval of andexanet alfa is expected soon.

3.1. Dabigatran antidote: idarucizumab

Idarucizumab is the first and only approved reversal agents specific for dabigatran. Idarucizumab is a humanized mouse monoclonal antibody that shows a structural mimicry to thrombin, in particular for the dabigatran binding site. Beyond lacking of enzymatic activity, idarucizumab differs from thrombin for a 350 -fold increase in dabigatran avidity [31]. Therefore, this antidote acts as a non-competitive inhibitor of dabigatran, that is able to bind it both in its free and thrombin-bound form. Dabigatran reversal is achieved by two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 min apart [32]. As for any antigen-antibody interaction, the onset of idarucizumab action is almost immediate and lasts for about 4 h until the renal clearance of the idarucizumab-dabigatran complexes, thus preserving the restored physiological haemostasis even after its elimination [30]. Three randomized phase I studies tested its safety, tolerability, efficacy and pharmacokinetics in healthy volunteers and subjects with typical characteristics of general population in terms of age, BMI, race, sex and renal impairment [33,34]. The promising findings on idarucizumab risk-benefit profile arising from phase I trials supported the development of idarucizumab until the completion of the REVERSE-AD phase III trial [32]. This multicenter, prospective, single-cohort trial evaluated the effect of idarucizumab in clinical emergency/urgency settings. The study enrolled 503 patients on dabigatran treatment judged by the investigator to require rapid anticoagulant reversal, either because of active bleeding or the need for invasive procedures. The study population primarily included elderly patients (mean age 78 years) with multiple comorbidities, in most cases treated because of NVAF (95%). Most common sites of bleeding were gastrointestinal (45.5%) and intracranial (32.6%), about one fourth of events were related to trauma. Among procedures requiring urgent reversal of dabigatran, the most common included abdominal surgery for hernia repair or infections (24.3%) and fractures (20.3%). Efficacy analysis was performed by considering only patients with a baseline prolonged diluted thrombin time (dTT) or ecarin clotting time (ECT), corresponding to 91,7% of the whole study population. Idarucizumab reversed dabigatran anticoagulant effect within 4 h in all patients (95% CI: 100–100), as measured by the diluted thrombin time (dTT) and the ecarin clotting time (ECT). Moreover, from a clinical point of view, bleeding cessation occurred after a median time of 2,5 h from antidote administration, whereas urgent surgery procedures could be initiated after a median of 1,6 h, ensuring a periprocedural haemostasis that was defined as normal in 93.4% of patients. The rate of thrombotic events was 4.8% within 30 days [32]. No prothrombotic events of idarucizumab were documented, while anti-idarucizumab antibodies were detected in 5.6% of patients, but only 9 of these 28 patients developed the antibodies during treatment and the titers were generally low. There were 3 potential hypersensitivity events reported, including a rash, vomiting and loss of consciousness, and hypotension. In the first two cases there were alternative causes for these events, the third event was interpreted as an anaphylactic reaction. A surveillance program, named RE-VECTO, is currently underway to collect post-approval data about idarucizumab usage patterns in real world clinical practice settings [35]. This registry may increase the awareness on the effectiveness of this antidote also in emergency scenarios other than those included in the REVERSE-AD trial.

3.2. Factor Xa inhibitors antidote: andexanet alfa

Andexanet alfa is a bioengineering product, created for the specific reversal of both direct and indirect FXa inhibitors. It is a human recombinant FXa variant, derived from the wild type form by removing a gamma-carboxyglutamic acid-rich (Gla) domain and introducing a missense mutation in the active binding site. These structural