Specific reversal agents in acute stroke

Senta Frol, M.D., Ph.D.[1,2]

[1] Dept of Vascular Neurology, University Medical Center Ljubljana, Ljubljana, Slovenia
[2] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

OPEN ACCESS

Correspondence:
Senta Frol
senta.frol@kclj.si

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 19 May 2024
Accepted: 3 June 2024
Published: 25 June 2024

Citation:
Frol S. Specific reversal agents in acute stroke
563=66-67 (2024): 72-76
DOI: 10.21857/9e31lhzpkm

Abstract

Direct oral anticoagulants (DOACs) are first line therapy in primary and secondary stroke prevention in patients with non-valvular atrial fibrillation. Regardless of their use a minority of patients still suffer acute stroke (ischemic or hemorrhagic). Specific reversal agents changed concept of therapy in DOAC-treated patients with acute stroke. In this manuscript data on randomized controlled trials, real-world evidence and proposed standard operating procedures are summarized.

Keywords: specific reversal agents, acute stroke

Sažetak:

Specifični lijekovi za reverziju kod akutnog moždanog udara

Direktni oralni antikoagulansi (DOAC) prva su linija liječenja primarne i sekundarne prevencije moždanog udara u bolesnika s nevalvularnom fibrilacijom atrija. Bez obzira na njihovu primjenu, manji broj bolesnika još uvijek pati od akutnog moždanog udara (ishemijskog ili hemoragijskog). Specifični antagonisti promijenili su koncept terapije u bolesnika s akutnim moždanim udarom liječenih DOAC-OM. U ovom rukopisu sažeti su podaci o randomiziranim kontroliranim ispitivanjima, stvarnim dokazima i predloženim standardnim operativnim postupcima.

Ključne riječi: specifični lijekovi za reverziju, akutni moždani udar

1 Introduction

Efficacy and safety of direct oral anticoagulants (DOACs) were proved in randomised controlled trials (RCTs) in patients with nonvalvular atrial fibrillation (AF) (1-4) therefore DOACs are suggested as first line therapy in primary and secondary stroke prevention in patients with non-valvular AF. Dabigatran is a thrombin inhibitor and its efficacy and safety was proved in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study (1). Rivaroxaban, apixaban and edoxaban are factor Xa inhibitors and their efficacy and safety were proven in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study (2), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study (3) and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (ENGAGE-AF) study (4), respectively.
Number of DOAC treated patients is rising up rapidly.
Despite safe and effective DOAC profile 1-2% of DOAC-treated patients per year suffer acute ischemic stroke (AIS) (1-4) and 0,1-0,2% per year intracranial haemorrhage (ICH)) (1-4).

2 Treatment of AIS and ICH

Successful revascularization therapy is gold standard treatment in patients with AIS. Intravenous thrombolysis (IVT) is first line therapy in AIS (5), importantly the higher efficacy if given promptly. In patients suffering AIS due to large vessel occlusion (LVO) endovascular treatment (EVT) is indicated (5). According to SWIFT-DIRECT (6) and DIRECT-SAFE (7) trials non-omitiing IVT prior EVT is suggested.
In patients suffering ICH efficient blood pressure control with its acute lowering below 140 mmHg systolic, hematoma growth prevention, normalization of anticoagulant activity and neurosurgical procedures, are suggested as first-line treatment strategies.

3 Specific reversal agents for DOACs

Two specific reversal agents for DOACs are in use.
Idarucizumab is a specifc reversal agent for dabigatran which enables complete and immediate reversal of its anticoagulant activity (8). It is a monoclonal antibody with very high affinity for dabigatran. It is ready to use as a bolus in a dose of 5 grams intravenously (i.v.) (8). Safety and efficacy of its use was proven in the REVERSal Effects of idarucizimab on Active Dabigatran (RE-VERSE AD) study (8) showing no thrombotic complications and low mortality rate. Use of idarucizumab is indicated in dabigtran-treated patients suffering life-threatening or uncontrolled bleedings or are in need of urgent interventions.
Andexanet alfa (AA) is a specific reversal agent for factor Xa inhibitors. It is a recombinant modified factor Xa inhibitor with similar binding affinity to that of factor Xa (9). It requires reconstitution prior to i.v. administration by bolus and 2 hours continuous infusion (9). We have two doses regarding the type, dose and last dose of factor Xa inhibitor taken. Efficacy and safety of AA use was proved in the Andexanet Alfa, a Novel Antidote to the Anticoagulation effects of FXa inhibitors (ANNEXA-4) trial (9). Importantly, 10% of patients in the ANNEXA-4 trial suffered thrombotic events (9). Use of AA is currently indicated for use in apixaban and rivaroxaban-treated patients suffering from life-threatening or uncontrolled bleedings (9), and not yet for edoxaban-treated patients. In the prospective ANNEXA-I randomized clinical trial (RCT) patients on edoxaban were also included. Due to high hemostatic efficacy in ICH patients treated with AA ANNEXA-I trial was stopped prematurely in June 2023 (10). Thrombotic events were reported at identical levels (10.3%) as for the ANNEXA-4 trial.

4 Treatment of AIS and ICH in DOAC-treated patients

European stroke organisation (ESO) (5) and European Heart Rhythm association (EHRA) guidelines (11) suggest the use of idarucizumab in dabigatran-treated patients if there are no other contraindications for IVT and if last dabigatran intake was <48 hours prior symptoms of AIS and oppose to AA use prior IVT in patients taking factor Xa inhibitors suffering AIS if last intake of rivaroxaban and apixaban was <48 hours prior sympotms of AIS (5, 11).
AHA/ASA, EHRA and ESO guidelines recommend idarucizumab application in dabigatran-treated patients suffering ICH and AA in rivaroxaban and apixaban-treated patients suffering ICH, respectively (11-13).

5 Real-world data on idarucizumab use in dabigatran-treated patients with acute stroke

5.1 Real-world data on idarucizumab use in dabigatran-treated patients with AIS

There is a growing body of published real-world cases on idarucizumab use in dabigatran-treated patients with AIS providing data on efficacy and safety of its treatment. In a cohort published by Kermer et al (14) authors included 80 patients treated with idarucizimab before IVT. Clinical improvement was found in 78.1% of patients with a median 7-point improvement in National Institutes of Health Stroke Scale (NIHSS) score. No bleeding complications or thrombotic events were reported and mortality rate was 3.75% (14). In year 2021 we published a systematic review analysing real-world data on efficacy and safety of idarucizumab use before IVT in dabigatran-treated patients with AIS (15). Rates of haemorrhagic transformation (HT), symptomatic intracranial haemorrhage (SICH), mortality and NIHSS

reduction were comparable with previously published studies in non-anticoagulated patients regardless of age and stroke severity upon admission (15). Additionally, we found that admission NIHSS score appeared to be an independent predictor of mortality (15). These data were updated by the summary of new real-world data of idarucizumab use in AIS until 22/07/2022, additionaly confirming the safety and efficacy of this treatment (16). In a narrative review just published in Frontiers in Neurology (17) we summarized all the available real-world evidence and importantly we discussed the relevance and importance of idarucizumab treatment in AIS with an SOP provided (17). Importantly, in an international, multicentre, retrospective cohort study done by Meinel et al (18) authors evaluated the risk of SICH associated with the use of IVT in DOAC-treated patients including patients treated with dabigatran receiving idarucizumab before IVT. Authors concluded that recent use of DOACs was not associated with increased risk of SICH development, regardless of idarucizumab reversal in dabigatran-treated patients (18).

5.2 Real-world data on idarucizumab use in dabigatran-treated patients with ICH

There is a growing body of reassuring real-world data on low mortality rates and low thrombotic complications in dabigatran-treated patients suffering ICH in whom idarucizimab was used (14, 19).

In a cohort published by Kermer et al (14) authors included 40 patients treated with idarucizimab due to ICH. Authors reported a median 4-point improvement in NIHSS at discharge, 60% of patients reached modified Rankin score ≤3 at discharge, hematoma expansion occurred in 3 patients and mortality rate was 15% (14).

In our systematic review published in 2021 (19) we analysed real-world data on safety of idarucizimab use in ICH. Our analysis provided clinically relevant quantitative data regarding in-hospital mortality in idarucizumab/dabigatran-treated patients with ICH, which was estimated to be 9.7-11.4% (19). In our paper published in year 2023 we provided an SOP of idarucizimab treatment in dabigatran-treated patients with ICH (16). Importantly, in our just published narrative review safety of idarucizumab treatment in ICH was additonaly confirmed (17).

6 Real-world data on AA use in dabigatran-treated patients with acute stroke

6.1 Real-world data on AA use in dabigatran-treated patients with AIS

As already mentioned current guidelines oppose to AA use before IVT in apixaban and rivaroxaban-treated patients with AIS therefore data on this topic are lacking.

6.2 Real-world data on AA use in dabigatran-treated patients with ICH

There is a growing body of real-world data on AA use in rivaroxaban and apixaban-treated patients suffering ICH (20, 21). Real-world data confirms AA efficacy with good/excellent hemostatic efficacy and low mortality rate (20). The major concern are thrombotic events as already expressed and found in ANNEXA-4 (9) and ANNEXA-I (10) trials. Importantly, use of AA is not indicated prior neurosurgery if done in 12 hours after AA application (9).

8 Standard operating procedures (SOP) for specific reversal agents use in DOAC-treated patients with acute stroke

8.1 SOP on idarucizumab use in dabigatran-treated patients with acute stroke

We proposed an SOP on idarucizumab use in dabigatran-treated patients with acute stroke (AIS and ICH) in our manuscript published in Journal of Thrombosis and Thrombolysis (16) and additionally explained it in our recently published narrative review in Frontiers in Neurology (17). We proposed that decision-making on the use of idarucizumab should be based on three relevant pieces of information: last time of dabigatran intake, special laboratory exams and renal function (16, 17). If dabigatran intake was less than 48 h before AIS symptoms onset or if laboratory exams are abnormal or if renal function is impaired or if there is uncertain value/time of last dabigatran intake and if the patient is an eligible candidate lacking other contraindications for IVT, patients should be treated with IVT after idarucizumab reversal (16, 17). In case of ICH, we suggested idarucizumab application if dabigatran intake was less than 48 hours before symptom onset or if laboratory exams are abnormal or if renal function is impaired or if there is uncertain value/time of last dabigatran intake (16, 17).

8.1 SOP on AA use in rivaroxaban and apixaban-treated patients with acute stroke

We proposed an SOP on AA use in rivaroxaban and apixaban-treated patients with acute stroke (AIS and ICH) in our leading article published in CNS Drugs (20). We suggested a decision--making on the use of AA based on three relevant pieces of information: (i) time of last Xa-inhibitor intake, (ii) special laboratory examinations, and (iii) renal function (20). AA application should be considered if the Xa inhibitor was taken within the last 48 h or if the time of last intake is unknown/uncertain or if the renal function is impaired or coagulation parameters are outside normal range. Low dose consisting of a bolus of 400 mg of AA followed by an infusion of 480 mg over 120 min is recommended if the last rivaroxaban/apixaban dose was taken ≥ 8 h ago (independent of dosage) or if the last dose was ≤ 5 mg for apixa-

ban and ≤ 10 mg for rivaroxaban, independent of time interval since last intake (https://www.ema.europa.eu/en/documents/product-infor mation/ondexxya-epar-product-information_en-1.pdf) and the high-dose regimen consisting of an 800 mg bolus followed by a 960 mg continuous infusion over 120 min is indicated only if the interval since last intake is 5 mg for apixaban or > 10 mg for rivaroxaban, respectively (https://www.ema. europa.eu/en/documents/product-information/ondexxyaepar-product--information_en-1.pdf) (20).

8 Conclusions

Number of DOAC treated patients is rising up rapidly. Despite regular DOAC use a minority of patients suffer AIS or ICH. Specific reversal agents for DOACs changed therapeutic strategies in DOAC-tretaed patients suffering acute stroke. Guidelines recommend use of idarucizumab in dabigatran-treated patinets with AIS and ICH and AA use for rivaroxaban and apixaban-treated patients suffering ICH.

Disclosures

Funding: No external funding was used in the preparation of this manuscript.

Conflict of interest: S.F. received speaker´s honoraria from Boehringer Ingelheim and AstraZeneca. Other than that, S.F. has no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data availability statement: Data sharing not applicable to this article as no datasets were generated in preparing this review of the literature.

Ethics approval: The present research complies with the guidelines for human studies, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Code availability: Not applicable.

References

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. (2009) 361:1139-51. doi: 10.1056/NEJMoa0905561.
2. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. (2011) 365:883-891.
3. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. (2011) 365:981-992.
4. Kaba RA, Ahmed O, Cannie D. ENGAGE AF: Effective anticoagulation with factor Xa in next generation treatment of atrial fibrillation. Glob Cardiol Sci Pract. (2013) 2013:354-6.
5. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J. (2021) 6:I-LXII.
6. Marnat G, Kaesmacher J, Buetikofer L, et al; SWIFT--DIRECT investigators. Interaction between intravenous thrombolysis and clinical outcome between slow and fast progressors undergoing mechanical thrombectomy: a post--hoc analysis of the SWIFT-DIRECT trial. J Neurointerv Surg. (2023) 16:45-52.
7. Mitchell PJ, Yan B, Churilov L, et al; DIRECT-SAFE Investigators. DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval versus Standard Bridging Therapy. J Stroke. (2022) 24:57-64.
8. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. (2017) 377:431-441.
9. Connolly SJ, Crowther M, Eikelboom JW, et al.; ANNEXA-4 Investigators. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. (2019) 380:1326-1335.
10. Connolly SJ. Randomized trial of andexanet alfa versus usual care in patients with acute intracranial hemorrhage while on an oral factor Xa inhibitor: ANNEXa-I [presentation]. In: Presented at the World Stroke Congress (WSC); 10–12 October, 2023; Toronto (ON).
11. Steffel J, Collins R, Antz M, et al; External reviewers. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. (2021) 23:1612-1676.
12. Greenberg SM, Ziai WC, Cordonnier C, et al; American Heart Association/American Stroke Association. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke. (2022) 53:e282-e361.
13. Christensen H, Cordonnier C, Kõrv J, et al. European Stroke Organisation Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage. Eur Stroke J. (2019) 4:294-306.

14. Kermer P, Eschenfelder CC, Diener HC, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany-Updated series of 120 cases. Int J Stroke. (2020) 15:609-618.
15. Frol S, Sagris D, Pretnar Oblak J, et al. Intravenous Thrombolysis After Dabigatran Reversal by Idarucizumab: A Systematic Review of the Literature. Front Neurol. (2021) 12:666086.
16. Frol S, Oblak JP, Šabovič M, et al. Standard operating procedure for idarucizumab reversal of dabigatran anticoagulation in ischemic and hemorrhagic stroke. J Thromb Thrombolysis. (2023) 55:506-518.
17. Frol S, Pretnar Oblak J, Šabovič M, et al. Idarucizumab in dabigatran-treated patients with acute stroke: a review and clinical update. Front. Neurol. (2024) 15:1389283.
18. Meinel TR, Wilson D, Gensicke H, et al; International DOAC-IVT, TRISP, and CRCS-K-NIH Collaboration; DOAC-IVT Writing Group; Kägi G, Engelter S, Nolte CH, Kallmünzer B, Michel P, Kleinig TJ, Fink J, Rønning OM, Campbell B, Nederkoorn PJ, Thomalla G, Kunieda T, Poli K, Béjot Y, Soo Y, Garcia-Esperon C, Ntaios G, Cordonnier C, Marto JP, Bigliardi G, Lun F, Choi PMC, Steiner T, Ustrell X, Werring D, Wegener S, Pezzini A, Du H, Martí-Fàbregas J, Cánovas-Vergé D, Strbian D, Padjen V, Yaghi S, Stretz C, Kim JT. Intravenous Thrombolysis in Patients With Ischemic Stroke and Recent Ingestion of Direct Oral Anticoagulants. JAMA Neurol. (2023) 80:233-243.
19. Frol S, Sagris D, Šabovič M, et al. Dabigatran Reversal With Idarucizumab and In-Hospital Mortality in Intracranial Hemorrhage: A Systematic Review of Real-Life Data From Case Reports and Case Series. Front Neurol. (2021) 12:727403.
20. Frol S, Oblak JP, Šabovič M, et al. Andexanet alfa to reverse the efect of factor Xa inhibitors in intracranial hemorrhage. CNS Drugs. (2023) 37(6):477–87.
21. Frol S, Oblak JP, Šabovič M, et al. Andexanet Alfa: What We Have Learned from Clinical Trials and Real-World Data. CNS Drugs. (2024) 38(3):163-168.