Journal of Neurology (2019) 266:2807–2811
https://doi.org/10.1007/s00415-019-09492-w

ORIGINAL COMMUNICATION

Idarucizumab administration in emergency situations: the Munich Registry of Reversal of Pradaxa® in clinical routine (MR REPAIR)

Clemens Küpper[1] · Katharina Feil[1,2] · Matthias Klein[1] · Regina Feuerecker[1] · Marc Lücking[3] · Florian Thanbichler[3] · Dennis Dietrich[4] · Irene Zerkaulen[5,6] · Mitja Jandl[7] · Martin Marziniak[7] · Holger Poppert[8,9] · Silke Wunderlich[8] · Helge Topka[3] · Marianne Dieterich[1,2,10] · Lars Kellert[1]

Received: 21 June 2019 / Revised: 28 July 2019 / Accepted: 30 July 2019 / Published online: 2 August 2019

Abstract

Objectives To evaluate daily life management and functional outcome of Idarucizumab administration in case of emergency situations in patients with Dabigatran treatment.

Design Multicenter observational registry study.

Setting All hospitals with full neurological departments ($n=6$) in Munich, Germany

Included patients All patients treated with Idarucizumab from 01/2016 to 03/2019.

Analyzed data Indication and application of Idarucizumab, demographics and clinical parameters, and further interventions and treatments; clinical outcome was assessed with the modified Rankin scale (mRS) at 3 months after Idarucizumab administration

Results Idarucizumab was administered to 32 patients for severe bleeding complications and ischemic strokes, more precisely for the following specific indications: intracranial bleeding (17 patients, 53%), ischemic stroke (8 patients, 25%), gastrointestinal bleeding (3 patients, 9%), femoral fracture, aortic dissection, and abdominal trauma and ileus (1 patient each, 3%). Additional coagulation management was performed in 7 patients (22%). Nine patients (28%) underwent emergency surgery. Seven patients (22%) received Idarucizumab before intravenous thrombolysis due to ischemic stroke and 4 of these 7 patients (13%) received mechanical thrombectomy in addition. Indication was mainly based on the history of Dabigatran intake and was irrespective of laboratory testing. At follow-up, 25% of the investigated patients had a mRS 0–2, while 25% had an unfavorable outcome (mRS 4–5). Mortality was 31%.

Conclusion In our study, we have shown that the administration of Idarucizumab is a rare intervention and restricted to patients with severe bleeding complications or ischemic stroke. The clinical outcome of patients who received Idarucizumab in emergency situations was poor.

Keywords Idarucizumab · Intracerebral hemorrhage · Ischemic stroke · Acute stroke · Oral anticoagulation · Dabigatran · Emergency · Emergency surgery

✉ Clemens Küpper
Clemens.Kuepper@med.uni-muenchen.de

[1] Department of Neurology, Ludwig Maximilians University, Campus Großhadern, Marchioninistraße 15, 81377 Munich, Germany

[2] German Center for Vertigo and Balance Disorders, Ludwig Maximilians University, Munich, Germany

[3] Department of Neurology Bogenhausen, Munich Hospital, Munich, Germany

[4] Department of Neurology Harlaching, Munich Hospital, Munich, Germany

[5] Department of Neurology, Helios Hospital Munich West, Munich, Germany

[6] Department of Neurology, Helios Amper Hospital Dachau, Dachau/Munich, Germany

[7] Department of Neurology, Kbo-Isar-Amper-Hospital Munich East, Munich, Germany

[8] Department of Neurology, University Hospital rechts der Isar, Technical University, Munich, Germany

[9] Department of Neurology, Helios Dr. Horst Schmidt Hospitals, Wiesbaden, Germany

[10] Munich Cluster of Systems Neurology (SyNergy), Munich, Germany

Introduction

Dabigatran (Pradaxa®, Boehringer Ingelheim, Ingelheim am Rhein, Germany) was shown to be an effective and safe oral anticoagulation (OAC) for prevention of stroke in nonvalvular atrial fibrillation (AF) and for prevention and treatment of systemic embolism in venous thromboembolism [1, 6]. However, OAC with Dabigatran bears the potential risk of major bleeding of approximately 2.4%/year [10]. In addition, OAC is a contraindication for intravenous thrombolysis (IVT) in case of acute ischemic stroke, and therefore, it is a substantial restriction for acute treatment in those patients. The possibility to neutralize direct oral anticoagulants with specific antagonists appears to be crucial for emergency situations. Idarucizumab (Praxbind®, Boehringer Ingelheim, Ingelheim am Rhein, Germany), a humanized monoclonal antibody fragment directed against the direct thrombin inhibitor Dabigatran, can rapidly reverse its anticoagulant effect [4]. Whether Idarucizumab improves clinical outcome compared to placebo is not known, because those trials are lacking. Overall mortality rate after 3 months in patients treated with Idarucizumab due to emergency situations was shown to be about 19% based on a phase III trial and an observational cohort study [4, 8]. In addition, current knowledge about Idarucizumab in daily clinical practice is only available from multiple case reports summarized in a review [9] and several case collections [2, 3, 5, 7]. However, only two publications on Idarucizumab use in acute ischemic stroke patients give systematic data on long-term functional outcome after treatment with Idarucizumab [2, 5]. The aim of the "Munich Registry of Reversal of Pradaxa® in clinical routine (MR REPAIR)", a multicenter observational registry study, was to systematically analyze the application of Idarucizumab in emergency situations in daily clinical practice and to assess the long-term clinical outcome of patients who received Idarucizumab.

Materials and methods

Study design and population: MR REPAIR is a multicenter observational registry study performed in Munich, a city with approximately 1.3 million inhabitants in the South of Germany. Study centers are all six hospitals with full neurological departments with stroke unit and emergency service including both university hospitals, all but one supra-regional and all regional trauma centers in Munich. Five hospitals with local trauma centers and one supra-regional trauma center did not participate as study centers. From 01/2016 until 03/2019, all patients treated with Idarucizumab were included to the registry either retrospectively (01/2016–01/2017) or prospectively (02/2017–03/2019), but only patients on Dabigatran were further analyzed. Consequently, one patient on Apixaban who had received Idarucizumab accidentally was excluded from the detailed analysis in this publication. To ensure that all patients who received Idarucizumab were included, the dispensary of all participating hospitals contacted the local coordinator in case of a reorder of Idarucizumab. Data about indication and application of Idarucizumab, demographics and clinical parameters, and further interventions and treatments as well as the partial thromboplastin time (pTT) on admission were collected by treating physicians and from medical charts. Follow-up at 3 months after Idarucizumab administration was assessed with the modified Rankin scale (mRS) by an experienced neurologist either during an outpatient clinical visit or by phone call.

Statistical analysis: normally, distributed data are presented as mean ± standard deviation (SD). Non-normally distributed data are presented as counts and percentages. The figure was designed with Microsoft Excel 2016 ®.

Results

Patient characteristics

In total, 32 patients (mean age ± SD 78 ± 9 years, 10 females) were included (see Table 1). Thus, approximately 10 patients per year received Idarucizumab in the Munich area (approx. 0.8 administrations/100 000 inhabitants/year). Premorbid functional status was good with functional independence (premorbid mRS 0–3) of a majority of 27 patients (84%) (see Fig. 1). Indication for Dabigatran was prophylaxis of ischemic stroke due to AF in all patients. Five patients (16%) took antiplatelet drugs additionally at the time of the emergency event. For individual dosages of Dabigatran and antiplatelet drug intake, see Table 1.

Laboratory examinations

The partial thromboplastin time (pTT) prior to Idarucizumab administration was available in 29 patients (91%). It was elevated in 17 of those 29 patients (53%) indicative of therapeutic Dabigatran blood levels, but also all 12 patients (38%) with normal pTT received Idarucizumab.

Indication of Idarucizumab

All patients received the full dosage of 5 g Idarucizumab. A majority of 25 patients (78%) were administered Idarucizumab because of a CNS emergency: 17 patients had

Table 1 Characteristics of 32 patients treated with Idarucizumab

Patient characteristics ($n=32$)	Value
Age (years), mean ± SD	78 ± 9
Female, *n* (%)	10 (31)
Indication for oral anticoagulation	Value
Atrial fibrillation, *n* (%)	32 (100)
Oral anticoagulation: Drug and dose	Value
Dabigatran 150 mg BID, *n* (%)	11 (34)
Dabigatran 110 mg BID, *n* (%)	16 (50)
Dabigatran 75 mg BID, *n* (%)	2 (6)
Dabigatran, dose not known, *n* (%)	3 (9)
Antiplatelet drugs: Drug and dose	Value
ASS 100 mg QD, *n* (%)	3 (9)
Clopidogrel 75 mg QD, *n* (%)	2 (6)
Unknown, *n* (%)	3 (9)
Indication for Idarucizumab and dose	Value
Intracranial bleeding, *n* (%)	17 (53)
Ischemic stroke, *n* (%)	8 (25)
Gastrointestinal bleeding, *n* (%)	3 (9)
Femoral fracture, *n* (%)	1 (3)
Aortic dissection, *n* (%)	1 (3)
Abdominal trauma, *n* (%)	1 (3)
Ileus, *n* (%)	1 (3)
Idarucizumab dose 5 g, *n* (%)	32 (100)
Partial Thromboplastin Time (pTT) prior to Idarucizumab administration	Value
n (%)	29 (91)
Above normal range, *n* (%)	17 (53)
Concomitant therapy	Value
Additional coagulation management, *n* (%)	7 (22)
Emergency surgery, *n* (%)	9 (28)
Intravenous thrombolysis for ischemic stroke, *n* (%)	7 (22)
Mechanical thrombectomy for ischemic stroke, *n* (%)	4 (13)
Endoscopy, *n* (%)	1 (3)
Resuscitation, *n* (%)	1 (3)

SD indicates standard deviation, *BID* bis in die (twice a day), *QD* Quaque die (daily)

intracranial bleeding (53%) and 8 patients had ischemic stroke (25%). Gastrointestinal bleeding resulted in Idarucizumab administration in 3 patients (9%). Idarucizumab was administered one each (3%) for femoral fracture, aortic dissection, abdominal trauma, and ileus. Emergency surgery was necessary in 9 patients (28%). 7 patients (22%) with ischemic stroke were treated with IVT and among those, 4 patients (13%) received mechanical thrombectomy (MT) in addition. No intracranial bleeding was observed in these patients after IVT/MT. In one additional patient with ischemic stroke (3%), systemic thrombolysis was stopped after the initial bolus of Alteplase® as the initially assumed time of symptom onset turned out to be wrong. Endoscopy was performed on 1 patient (3%) with gastrointestinal bleeding, while another (3%) received cardiopulmonary resuscitation due to hemorrhagic shock.

Further coagulation management

In 7 patients (22%), further coagulation management procedures were performed including the administration of fresh frozen plasma, prothrombin complex concentrate, fibrinogen, tranexamic acid, platelet concentrate, and red blood cell transfusion (see Table 1).

Clinical outcome

At follow-up, a minority of 8 patients (25%) had a mRS 0–2. Three patients (9%) were disabled but independent (mRS 3). Eight patients (25%) had an unfavorable outcome with a mRS 4–5 and 10 patients (31%) died [including 5 patients (16%) with intracranial bleeding and 2 patients with ischemic stroke (6%)] (see Fig. 1).

Discussion

The major results of our study were as follows: First, in the six hospitals with full neurological departments in Munich, a city with about 1.3 million inhabitants, Idarucizumab was administered with a rate of 0.8/100 000

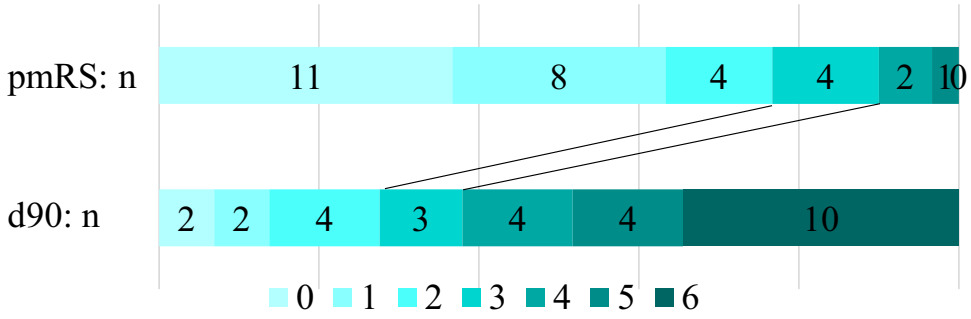

Fig. 1 Patients' functional outcome based on the modified Rankin scale (mRS): premorbid ($n=30$, 2 missing) and on day 90 after Idarucizumab administration ($n=29$, 3 lost to follow up)

inhabitants/year mostly to patients with CNS emergencies. Second, the long-term functional outcome in a majority of the patients was poor with a mortality rate of 31%. Third, Idarucizumab was administered according to guideline recommendations in all cases with a dose of 5 g and applied only to patients with severe bleeding complications or ischemic strokes under treatment with Dabigatran. Idarucizumab administration in minor or moderate bleedings was not observed. Finally, Idarucizumab administration was guided by clinical information and the history of Dabigatran intake and was irrespective of laboratory tests.

In contrast to this study, a recent large cohort observational study in 2019 had shown a mean annual administration rate of about 29 in The Netherlands, a country with about 17 million inhabitants, which means more than 10 times more inhabitants than in Munich [8]. Thus, in our study, Idarucizumab had been given more frequently (approx. four times). The mortality rate in the Dutch observational study on day 90 was 19% [8] similarly to the REVERSE-AD study [4], but lower than in our study. This might be related to the higher rate of patients with CNS emergencies (78% vs. 24% in the Dutch cohort study [8] and vs. 23% in the REVERSE-AD study [4]). Neither the Dutch observational study nor the REVERSE-AD study included functional outcome parameters [4, 8]. Only for ischemic stroke patients on Dabigatran who received Idarucizumab before acute stroke treatment, long-term functional outcome parameters are available from two publications: A retrospective nationwide Czech study with 13 patients and an Italian literature review on 37 published single cases reported good functional outcome (mRS 0–2) in 77% and 57% of the patients, respectively [2, 5]. In contrast, the rate of patients with a mRS 0–2 of our mixed cohort was only 25%. This discrepancy might indicate that Idarucizumab administration enables efficient acute stroke treatment with IVT and/or mechanical thrombectomy, but does not guarantee good clinical outcome in other emergency situations such as bleeding events.

Our study has some limitations: First, this was an observational study with a relatively low number of patients ($n = 32$) which might have caused bias to patients' selection and study results, especially regarding outcome parameters. In particular, half of the patients (16/32) had a pmRS > 2, thus could not reach a mRS 0–2 after the event which would usually be defined as a good clinical outcome. Second, reliable laboratory tests such as diluted thrombin time or ecarin-clotting time as control of Dabigatran intake were not available in a sufficient number of patients, and therefore, patients without significant Dabigatran levels might have been treated.

Conclusions

The current study showed that in daily life, the administration of Idarucizumab is a rare intervention and restricted to patients with severe bleeding complications or ischemic strokes. However, long-term functional outcome in patients after Idarucizumab administration in emergency situations was poor with a high mortality rate. The performance of a larger placebo-controlled study would be desirable to verify the effect of Idarucizumab administration on the long-term functional outcome of emergency patients.

Acknowledgements We thank all patients for their willingness to participate in our study.

Funding This research has been performed without specific funding.

Compliance with ethical standards

Conflicts of interest C.K, K.F., M.K., R.F., M.L., F.T., D.D., I.Z., M.J., M.M., H.P., S.W., H.T., and M.D. report no conflict of interest. L.K. has received funding for travel or speaker honoraria from Bayer Vital, Boehringer Ingelheim, Bristol-Meyer-Squibb, Daiichi Sankyo, and Pfizer outside of this study.

Ethical standards The study was approved by the Institutional Review Board of the University of Munich (project no. 15–075) and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients or their legal representatives gave written informed consent prior to their inclusion in the study.

References

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, R-LS Committee Investigators (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361:1139–1151
2. Giannandrea D, Caponi C, Mengoni A, Romoli M, Marando C, Gallina A, Marsili E, Sacchini E, Mastrocola S, Padiglioni C, Mazzoli T, Cenciarelli S, Ricci S (2019) Intravenous thrombolysis in stroke after dabigatran reversal with idarucizumab: case series and systematic review. J Neurol Neurosurg Psychiatry 90:619–623
3. Kermer P, Eschenfelder CC, Diener HC, Grond M, Abdalla Y, Althaus K, Berrouschot J, Cangur H, Daffertshofer M, Edelbusch S, Groschel K, Haase CG, Harloff A, Held V, Kauert A, Kraft P, Lenz A, Mullges W, Obermann M, Partowi S, Purrucker J, Ringleb PA, Rother J, Rossi R, Schafer N, Schneider A, Schuppner R, Seitz RJ, Szabo K, Wruck R (2017) Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany—a national case collection. Int J Stroke 12:383–391
4. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI

(2017) Idarucizumab for dabigatran reversal—full cohort analysis. N Engl J Med 377:431–441
5. Sanak D, Jakubicek S, Cernik D, Herzig R, Kunas Z, Mikulik R, Ostry S, Reif M, Rohan V, Tomek A, Veverka T (2018) Intravenous thrombolysis in patients with acute ischemic stroke after a reversal of dabigatran anticoagulation with idarucizumab: a real-world clinical experience. J Stroke Cerebrovasc Dis 27:2479–2483
6. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C, Investigators R-CIT (2014) Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 129:764–772
7. Tsai LK, Lin HJ, Chua SK, Liao PC, Yang YP, Chou PC, Lee CW, Lin MJ, Chen HM, Yeh JT, Li YH (2018) Real-world experience with idarucizumab to reverse anticoagulant effect in dabigatran-treated patients: report of 11 cases from Taiwan. J Stroke Cerebrovasc Dis 27:e27–e33
8. van der Wall SJ, van Rein N, van den Bemt B, Kruip M, Meijer K, Te Boome LCJ, Simmers TA, Alings AMW, Tieleman R, Klok FA, Huisman MV, Westerweel PE (2019) Performance of idarucizumab as antidote of dabigatran in daily clinical practice. Europace 21:414–420
9. Vornicu O, Larock AS, Dincq AS, Douxfils J, Dogne JM, Mullier F, Lessire S (2017) Idarucizumab for the treatment of hemorrhage and dabigatran reversal in patients requiring urgent surgery or procedures. Expert Opin Biol Ther 17:1275–1296
10. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, Noseworthy PA (2016) Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc 5:e003725