Clinical Neurology and Neurosurgery 181 (2019) 76–81

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

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

Dabigatran reversal by idarucizumab in the setting of intracranial hemorrhage: A systematic review of the literature

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ARTICLE INFO

Keywords:
Dabigatran
Idarucizumab
Intracranial hemorrhage
Reversal
Anticoagulation
Systematic review

ABSTRACT

Idarucizumab is the first Food and Drugs Administration (FDA) approved reversal agent for anticoagulant dabigatran, a direct thrombin inhibitor. Emerging evidence suggests idarucizumab can improve clinical outcome following dabigatran-associated hemorrhage, however, its specific use in intracranial hemorrhage has been poorly described. The aim of this study was to systematically review the available literature of idarucizumab in the setting of dabigatran-associated ICH to evaluate its efficacy in the stabilizing/resolving of the primary hemorrhage. A systematic search of 7 electronic databases from their earliest records to August 2018 was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. There were 864 articles identified for screening against selection criteria. The search identified 9 articles to be included in our analysis, describing hemorrhage outcomes in 23 dabigatran-associated cases of ICH managed by idarucizumab. Mean overall age was 76.2 years, with 43% females, and bleeding was subdural, subarachnoid and intracerebral in 43%, 13% and 43% cases respectively. Surgical intervention was pursued in 48% of cases. During the course of the hospitalization, the hemorrhages stabilized/resolved in 87% of patients, and worsened in 13%. In-hospital complications occurred in 4% of cases, and mortality occurred in 4% of cases as well. The available literature suggests that idarucizumab can be applied in the setting of ICH, for its therapeutic effect in patients presenting with dabigatran-associated ICH appears acceptable with no compromise to clinical safety. However, currently there is a paucity of data about various aspects that are involved in other aspects of ICH treatment, including recovery, that limits the significance of the current literature. As more evidence is published relating specifically to long-term ICH outcomes that have been treated by idarucizumab, we will be better placed to establish the optimal role of idarucizumab in the setting of dabigatran-associated ICH.

1. Introduction

Non-valvular atrial fibrillation (NVAF) has emerged as a significant health care threat in developed countries due to an aging population and an increasing number of people on anticoagulation. The number of prophylactically medicated patients is expected to rise dramatically, from 2 to 3 million individuals today to 5.6 million by 2050 in the United States alone [1,2]. This is of great importance because being anticoagulated renders patients at greater risk to life-threatening hemorrhage, including spontaneous and traumatic intracranial hemorrhage (ICH). Conservative estimates suggest that life-threatening ICHs occur in up to 4% of anticoagulated patients per year, which is up to 10 times greater than the general population [3–6]. Furthermore, it has been postulated that more than 50% of these ICHs are likely fatal, which is more than twice the normal risk [7].

Traditionally, vitamin K antagonist warfarin (Coumadin) has been used to anticoagulate NVAF patients with the intention to protect individuals from disabling stroke. In cases of warfarin-associated ICH, the anticoagulation effect can be rapidly attenuated by either prothrombin complex concentrates (PCC) with factor VII or fresh frozen plasma (FFP), and reversed effectively over time with vitamin K [8,9]. More recently, dabigatran (Pradaxa), which is a non-vitamin K antagonist oral anticoagulant (NOAC), was introduced as one of the alternatives to warfarin, with a pragmatic advantage of requiring less to no monitoring without compromising efficacy. This however, led to a clinical conundrum as reversal options for dabigatran at the time were limited: activated charcoal could bind to free dabigatran [10], and PCC [11] and recombinant factor VIIa [12] could increase endogenous thrombin

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https://doi.org/10.1016/j.clineuro.2019.04.013
Received 19 January 2019; Received in revised form 10 April 2019; Accepted 14 April 2019
Available online 15 April 2019
0303-8467/

generation similarly to that of warfarin, however these options did not reverse dabigatran completely [13].

In October 2015, the Food and Drug Administration (FDA) approved idarucizumab, a monoclonal antibody fragment specifically designed to target dabigatran, for its use in reversal of anticoagulation. Recently, the publication of the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) observational study demonstrated that idarucizumab can be used safely and effectively in managing all hemorrhage types, including ICH, although the specific outcomes of ICH subjects only were not detailed [14]. To date, there has been limited evidence reported on the use of idarucizumab in the setting of ICH only. The aim of this systematic review was to review the current literature to ascertain if idarucizumab is effective as a reversal agent in the setting of dabigatran-associated ICH. This will assist in elucidating whether or not idarucizumab should continue to be investigated in this specific and niche context.

2. Methods

This systematic review was conducted according to both PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [15,16]. In PICO format, we aimed to summarize the clinical course (outcome) in dabigatran-associated ICH (population) managed with idaricizumab (intervention); there was no comparator group. Electronic searches were performed using Ovid Embase, PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to August 2018. The literature was searched by using an algorithm employing the following keywords: “dabigatran” and “idarucizumab”. All identified articles were then systematically assessed against the inclusion and exclusion criteria by two independent reviewers (V.M.L. and K.P.). This was performed after the search protocol had been finalized.

Inclusion criteria used to screen all retrieved articles were 1) case report, case series, retrospective or prospective studies reporting patients receiving anticoagulant dabigatran who presented with image-confirmed ICH, and whose management included intentional anticoagulant reversal with idarucizumab, and 2) studies that provided hemorrhage outcome data at discharge. Definition of ICH included: subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICbH). Hemorrhage outcomes during hospitalization were categorized as either stable, resolved or worsened based on radiologic evidence. Stable was defined as no increase in hemorrhage size from presentation. Resolved was defined as no radiologic evidence of hemorrhage upon imaging. Finally, worsened was defined as radiologic enlargement of the hemorrhage with signs of clinical deterioration. The imaging modality of choice was computed tomography (CT). There was no etiological restriction on ICH, with both spontaneous and traumatic ICH included in this study. All study types were included to maximize yield. Exclusion criteria applied were as follows: 1) stroke-related, ischemic presentations, as well as all non-cranial hemorrhages, and 2) editorial, commentary, and review articles without granular data of individual patients. When institutions published duplicate studies with either overlapping or accumulating numbers of patients, the most complete report was included. Publications were limited to those involving adult human patients and those reported in English.

3. Results

3.1. search results

A total of 864 articles were identified for evaluation (Fig. 1). After the removal of 392 duplicate articles, the title and abstract of the remaining 472 articles were evaluated against the selection criteria. Full-text analysis was performed for 20 articles, in which 9 were assessed to be eligible for inclusion into this systematic review. This allowed us to summarize the final outcome at discharge of 23 ICH patients who were receiving dabigatran prior to ICH presentation, and whose management included idarucizumab, as detailed 2 case series [17,18] (n = 15), and 7 case reports [19–25] (n = 8) (Table 1). The observational RE-VERSE AD study by Pollack et al. [14] was not included for it did not report ICH-only hemorrhage outcomes, and two other articles [26,27] were excluded due to overlapping cohorts.

3.2. Demographic characteristics

Collectively, 23 dabigatran-associated ICH cases were pooled in this study, with 10 SDH, 3 SAH and 10 ICbH presentations (Table 1). There were 10 females (43%) and 13 males (57%), with an overall mean age of 76.2 years. Dabigatran was indicated in these patients for NVAF (21/23, 92%), valvular disease (1/23, 4%) and stroke prophylaxis (1/23, 4%). The median dose regimen was 110 mg bid, with 6 patients reported to be taking a higher dose of 150 mg bid. Etiology was clearly reported in 10 cases, where 5 were spontaneous, 4 caused by a fall, and 1 was due to a motor vehicle accident.

3.3. Clinical course

Complete details of clinical course are described in Table 2. In terms of idarucizumab regimen, all cases received 5 g of intravenous idarucizumab at presentation, with surgery pursued in 11/23 (48%) cases, and an additional 4000 IU PCC for 1 patient [22]. Mean activated partial thromboplastin time (aPTT) and thrombin time (TT) values pre-idarucizumab were 35.7 ± 10.1 and 107.2 ± 42.5 s respectively, and both significantly decreased to 26.0 ± 4.1 and 19.6 ± 4.9 s respectively post-idarucizumab where reported (Fig. 2). During hospitalization, radiographic surveillance indicated that hemorrhage of 20/23 (87%) patients had stabilized/resolved, with only 3/23 (13%) having experienced worsening. There was 1/23 (4%) in-hospital mortality events in this pooled cohort, reported by Kermer et al. [17] due to terminal ICH, and only 1/23 (4%) in-hospital adverse event of dysphagia reported [21]. Patients were all clinically stable at time of discharge, with median length of stay of 6 days (based on 7 cases only).

4. Discussion

Our systematic review highlights that the use idarucizumab is effective in reversing the anticoagulation effect of dabigatran in patients presenting specifically with ICH. A 5 g dose of idarucizumab was sufficiently effective to decrease/normalize anticoagulation parameters as inferred by aPTT and TT values across all presentations. Stabilization or resolution of hemorrhage occurred in 87% of cases in the pooled cohort with no medication-related adverse effects. The in-hospital mortality rate of 4% compares favorably to the corresponding rate of up to 30% in those ICH patients receiving dabigatran not treated by idarucizumab [28,29], as well as the 9% mortality rate reported for idarucizumab-reversed ICH by the RE-VERSE AD study [14]. These values are supportive of both the efficacy and safety of idarucizumab. However, there remains a number of aspects that require clarification before comprehensive recommendations should be able to be made.

4.1. Therapeutic potential

The optimal coagulation parameter(s) to evaluate idarucizumab in dabigatran-associated bleeding remains unclear. The more traditional aPTT parameter has been used in assessing warfarin reversal, however this measure has been shown to interact differently with dabigatran-associated blood than blood anticoagulated by other agents, which risks misleading conclusions that utilize those standard ranges [30,31].

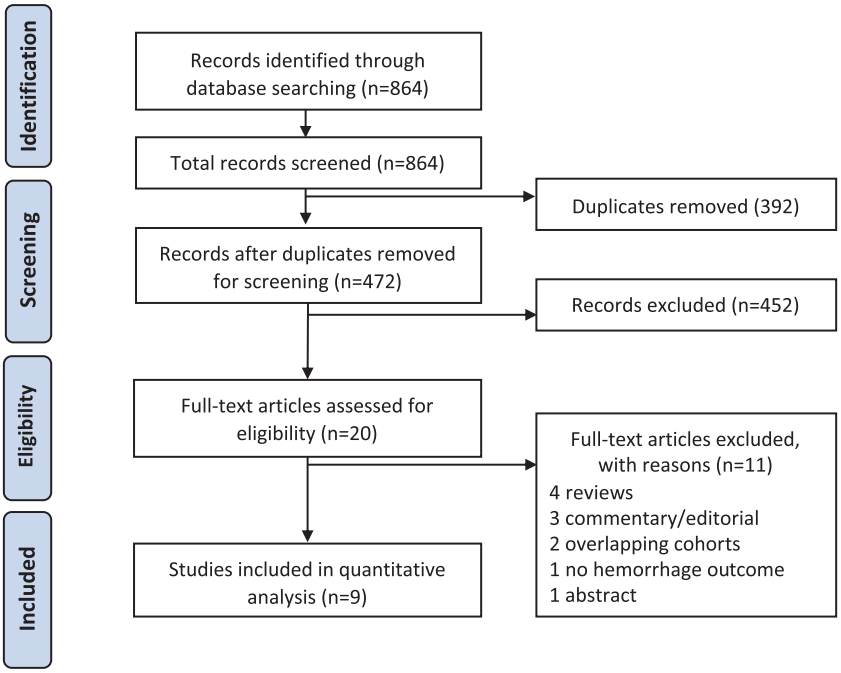

Fig. 1. Results of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) search strategy.

Table 1
Study and demographic characteristics. ICH, intracranial hemorrhage; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; ICbH, intracerebral hemorrhage; MVA, motor vehicle accident; NR, not reported.

						ICH presentation			
Study	Country	Design	Cases (n)	Mean age (yrs)	Females (n)	SDH	SAH	ICbH	Etiology
Arai et al. [19]	Japan	Case report	1	79	0	1	.	.	1 Fall
Balakumar et al. [20]	US	Case report	1	86	1	.	1	.	1 Fall
Edwards et al. [21]	Australia	Case report	2	70	0	2	.	.	1 MVA, 1 Fall
Gendron et al. [22]	France	Case report	1	80	0	1	.	.	1 Fall
Goriacko et al. [23]	US	Case report	1	79	0	.	.	1	1 Spontaneous
Hieber et al. [25]	Germany	Case report	1	83	1	1	.	.	1 Spontaneous
Kermer et al. [17]	Germany	Case series	12	75	6	3	1	8	NR
Quintavalla et al. [24]	Italy	Case report	1	82	1	1	.	.	NR
Vosko et al. [18]	Europe	Case series	3	73	1	1	1	1	3 Spontaenous
		Sum (% total)	23	76.2 (average)	10 (43%)	10 (43%)	3 (13%)	10 (43%)	.

Nonetheless, we note that in the reported ICH cases, there was a significant decrease in aPTT following idarucizumab administration. This could be independent of time from last dabigatran dose, as Hieber et al. [25] described their patient last took dabigatran 2.5 h before presentation, and Quintavalla et al. [24] had one case that took dabigatran 26 h before presentation, with both having favorable outcomes. Nonetheless, this remains anecdotal until more studies can report such a time frame.

Perhaps a more reliable and sensitive measure is the TT parameter due to the direct thrombin targeting by dabigatran, and thus be a superior marker of idarucizumab activity in hemorrhage [32,33]. Similarly, we note that there was a significant decrease in TT following idarucizumab administration as well in the reported ICH cases. Nevertheless, interpretation by either parameter based on the current data would indicate that idarucizumab is an effective agent in normalizing the coagulation profile of dabigatran-associated ICH.

An attraction of idarucizumab in the setting of ICH is not only its dabigatran reversing property, but also the speed at which this reversal apparently occurs, since quicker normalization of coagulation parameters is associated with improved outcomes in ICH [34,35]. Arai et al. [19] noticed decreased intracranial arterial bleeding and less tissue oozing intraoperatively only 5 min after drug administration. This correlates with the observation made in some case reports that showed a reduction in aPTT and TT profiles within the first hour after administration [21,24]. The respective values had returned to normal values by 2 h in the case reported by Gendron et al. [22], and remained normal for at least 24 h after administration in other case reports [18,23]. The case of Gendron et al. [22] reported normalized values up to 5 days after initial administration.

Additionally, there is promise that the ICH context does not require separate consideration from general hemorrhage management when surgical intervention is needed. An example of this is the time to surgery, with Edwards et al. [21] reporting that their two SDH cases proceeded to surgery 1.5 h after idarucizumab administration. This corresponds closely to the findings of the RE-VERSE AD study [14] where the authors noted that median time from idarucizumab administration to surgery to be 1.6 h across all hemorrhage sources, which highlights a rapid turnaround is indeed practically achievable in the setting of ICH specifically.

4.2. Clinical considerations

In the RE-VERSE AD study, all observed in-hospital thrombotic events occurred within the first 72 h after administration of a single

Table 2
Clinical course of each patient reported in all case series and reports. M, male; F, female; bid, twice a day; NVAF, non-valvular atrial fibrillation; ICH, intracranial hemorrhage; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; ICbH, intracerebral hemorrahage; CrCl, creatinine clearance; aPTT, activated partial thromboplastin time; TT, thrombin time; N, no; Y, yes. "." represents unreported data.

			Dabigatran		aPTT (s)		TT (s)						
Study	Case #	ICH Type	Regimen	Indication	Pre-idarucizumab	Post-idarucizumab	Pre-idarucizumab*	Post-idarucizumab	Surgery	Hemorrhage outcome during hospitalization	Complications	In-hospital mortality	Days to discharge (destination)
Arai et al. [19]	1	SDH	110 mg bid	NVAF	35	.	.	.	Y	Resolved	N	N	3 (Home)
Balakumar et al. [20]	1	SAH	75 mg bid	NVAF	30.8	.	.	.	N	Stable	N	N	6 (Rehabilitation)
Edwards et al. [21]	1	SDH	110 mg bid	NVAF	63	35.5	133.4	18.1	Y	Resolved	dysphagia	N	.
	2	SDH	110 mg bid	NVAF	48.4	28.6	.	16.5	Y	Resolved	N	N	.
Gendron et al. [22]	1	SDH	110 mg bid	NVAF	44.1	25	149	27.5	N	Stable	N	N	5 (Home)
Goriacko et al. [23]	1	ICbB	75 mg bid	Valve disease	32.6	24.9	.	.	Y	Resolved	N	N	.
Hieber et al. [25]	1	SDH	110 mg bid	NVAF	73.1	17.6	73.1	17.6	Y	Resolved	N	N	.
Kermer et al. [17]	1	SAH	150 mg bid	NVAF	30.3	20.7	120	18.1	4 Y, 8 N	Stable	N	N	.
	2	ICbB	150 mg bid	NVAF	26.5	22.7	53.4	18.2		Worsened	N	N	.
	3	ICbB	110 mg bid	NVAF	34	.	200	.		Stable	N	N	.
	4	ICbB	150 mg bid	NVAF	44	.	.	.		Worsened	massive bleeding	Y	.
	5	SDH	110 mg bid	NVAF	30	27	73.1	17.6		Stable	N	N	.
	6	SDH	110 mg bid	NVAF	47.3	29.9	.	.		Stable	N	N	.
	7	ICbB	110 mg bid	NVAF	44.2	.	150	.		Stable	N	N	.
	8	ICbB	110 mg bid	NVAF	30.3	23.9	81.6	20.6		Stable	N	N	.
	9	ICbB	110 mg bid	NVAF	32.6	28.2	77.8	.		Stable	N	N	.
	10	ICbB	110 mg bid	NVAF	.	.	119	.		Stable	N	N	.
	11	ICbB	150 mg bid	NVAF	22.4	25	.	.		Worsened	N	N	.
	12	SDH	150 mg bid	NVAF	28.8	25.3	93.3	19.1		Stable	N	N	.
Quintavalla et al. [24]	1	SDH	110 mg bid	NVAF	.	.	60	13.8	Y	Resolved	N	N	7
Vosko et al. [18]	1	SDH	110 mg bid	NVAF	49.9	.	.	19.2	Y	Resolved	N	N	5
	2	SAH	150 mg bid	Stroke	39	33	73.9	16.7	N	Resolved	N	N	9
	3	ICbH	110 mg bid	NVAF	.	.	150	32	N	Stable	N	N	7 (Rehabilitation)
Pooled total/ mean	*25*	–	–	–	*35.7*	*26.0*	*107.2*	*19.6*	*11/23 (48%) Yes*	*3 Worsened*	*2*	*1 Yes*	*6*

* Upper threshold limit reported where specific value not available.

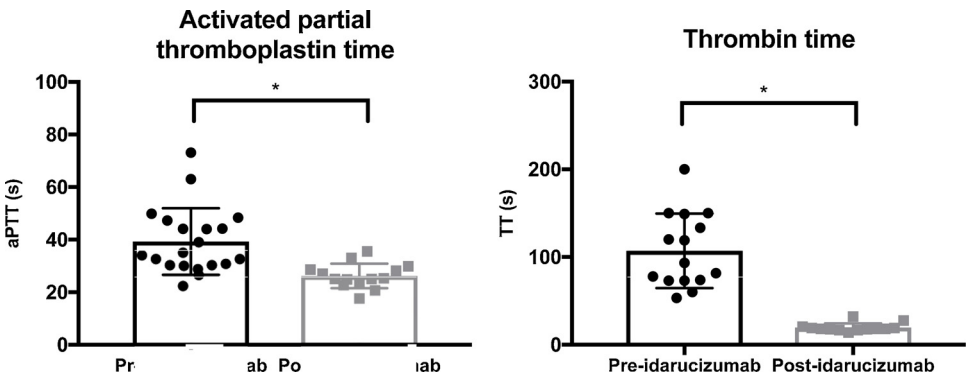

Fig. 2. Graphic representation of individual activated partial thromboplastin time (aPTT) and thrombin time (TT) values pre- and post-idarucizumab administration in dabigatran-associated intracranial hemorrhage (ICH). Data points represent individual values, and summary columns are presented as mean ± standard deviation. Unpaired *t*-test was used to identify significant difference between mean values ($P < 0.05$; represented by *). Statistical analysis performed using Prism 7 (GraphPad, USA).

bolus of idarucizumab [14]. All patients, except one, in this review had a unremarkable clinical course in-hospital, with zero thrombotic events reported. However, considering that the rate of clinically observed thrombotic events in the RE-VERSE AD study was 4.8% at 30 days, and 6.8% at 90 days for all types of hemorrhage, this may still have applied to some ICH patients reported in the case studies and series we have identified, as post-discharge follow-up up to 90 days was largely not reported [14]. Robust long-term data is currently lacking to assess 30- and 90-day safety in ICH-specific cases, and we note that the follow-up after discharge is only provided for 3 patients in the current literature, whom at 5 [19], 7 [21] and 9 [24] months had unremarkable courses.

The timing of restarting systemic anticoagulation with dabigatran after reversal by idarucizumab remains unclear. Idarucizumab has a half-life of 45 min and thus the clotting risk (which lead to initial indication of anticoagulation) can presumably be liable to resurface rapidly after ICH control and drug dissipation [36].The clinical question of when to recommence anticoagulation does not have a clear consensus answer as it requires a multidisciplinary, yet individualized, approach to the patient to ensure optimal outcome. More likely than not, workup of this will depend on both clinician preference and patient status and anticoagulation indications. There is anecdotal evidence of this inherent variability in the literature to date highlighting this uncertainty: Arai et al. [19] restarted dabigatran after 24 h, Gendron et al. [22] reported one case that restarted in 72 h, while Quintavalla et al. [24] withheld systemic anticoagulation completely, without reported issues at their last (10-month) follow-up.

Although the short period of time which is required to reverse dabigatran in general is impressive, concerns have been raised that this may not be sufficient in serious cases of ICH. [37] In the interim analysis of the RE-VERSE AD study, it was reported that the median time to cessation of bleeding was more than 11 h when serious ICHs were included [38]. Bridging more rapidly to fully reestablish coagulation capability via the application of blood-components (such as PCC) may offer idarucizumab even greater efficacy in cases of serious ICH. It has been argued that a transient increase in overall thrombotic risk is more acceptable if lifesaving hemostasis can more likely be achieved in serious bleeding circumstances [39]. The issue of finding the optimal dose to minimize the risk of incomplete anticoagulation-reversal also requires confirmatory studies, for it has been reported in non-ICH hemorrhages that a standard dose of 5 g was not always sufficient [40].

Finally, how financially feasible it is to utilize idarucizumab in various clinical settings of ICH is unclear. The Wholesale Acquisition Cost (WAC) of a single 5 g bolus of idarucizumab is reportedly priced at $3482.50 USD [41].This would be an expense that comes in addition to the investment in health care resources required in evaluating dabigatran-associated ICH in a timely fashion. Beyond this one needs to consider the logistics of a timely reversal by idarucizumab, which puts constraints on the availability of laboratory tests, imaging, and possible release and transfusion of additional blood products. It is estimated that up to 60% of patients managed by idarucizumab will require additional blood products during their primary management [14]. Thus, a cost-benefit analysis is needed to elucidate the best scenario in which idarucizumab can be optimally used in the day to day hospital setting.

4.3. Literature limitations

A significant gap in the knowledge reflected in the current literature is the lack of reporting of how idarucizumab compares directly to cases where reversal was attempted by other agents, such as PCC and FFP. Due to the limited number of cases reported outside the RE-VERSE AD study, in addition to the absence of a proper control arm in the study, the risk of selection bias for idarucizumab application reported in current publications on its use in ICH remains considerable [42].

By virtue of that fact that there is no randomized controlled trial (RCT) to date, it can only be speculated at the moment whether or not idarucizumab confers a statistically significant overall survival benefit compared to other approaches in patients sustaining an ICH on therapeutic dabigatran doses. There are limited measures that will be able to quantify this comparison, however one such avenue is the use of surgical outcomes involving blood replacement including operative blood loss and blood product usage in those managed surgically. Given 48% of cases were managed with surgery, these measures are not unreasonable to include in future post-marketing studies. Other coagulation-related parameters at time of anticoagulation reversal, such as diluted TT and Ecarin times (Ecarin clotting time, ECT; ecarin chromogenic assay, ECA,) would also prove insightful moving forward as idarucizumab becomes more available in treating ICH. In particular, the diluted TT parameter as a measure of dabigatran levels could prove useful in assessment for speed and duration of dabigatran suppression in these patients. Of all the studies, only Quintavalla et al. [24] reported this value before and after idarucizumab administration, noting a drastic drop from 183 to < 1 ng/mL.

One parameter in particular to investigate is the duration that anticoagulation reversal lasts for after 1 dose of idarucizumab. Although its half-life is less than 1 h, Goriacko et al. [23] reported normalized aPTT/TT at least 24 h after administration, and Gendron et al. [22] reported one case where normalized aPTT/TT values were observed up to 5 days after administration. No other study reported this trend, so more information is needed to better understand both drug effect and influence post-idarucizumab surveillance protocols. A method to infer clinical significance of such findings would be to perform, serial regular imaging to better define the association of radiologic response and coagulation parameters, for currently the literature is inconsistent in when and how often post-presentation imaging is performed. We recognize that as the current ICH data is so young, there are no reports in the literature have calling for implementation of new ICH protocols in response to this emerging data on idarucizumab, yet.

5. Conclusion

The current literature indicates that idarucizumab is an effective reversal agent of dabigatran with favorable complication and mortality

incidences, and thus should not be discounted in the management of dabigatran-associated ICH. Further investigation is justified in validating or refuting the pooled findings of this systematic review. Although RCTs would be optimal, it is more likely pragmatically observational cohort studies such as the RE-VERSE AS study are more realistic, with consideration for historic control groups if needed. There is a clear need to ascertain the ideal role of idarucizumab in ICH management, as well as to identify specific hematological and clinical practice parameters that will assist in assessing idarucizumab-assisted recovery. Furthermore, a proper cost-benefit analysis with post-marketing study will aid in establishing the optimal use pattern of this novel drug in the hospital setting.

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