Clinical Pharmacokinetics and Pharmacodynamics of Desmoteplase

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Abstract
Desmoteplase is a bat (Desmodus rotundus) saliva-derived fibrinolytic enzyme resembling a urokinase and tissue plasminogen activator. It is highly dependent on fibrin and has some neuroprotective attributes. Intravenous administration of desmoteplase is safe and well tolerated in healthy subjects. Plasma fibrinolytic activity is linearly related to its blood concentration, its terminal elimination half-life ranges from 3.8 to 4.92 h (50 vs. 90 μg/kg dose). Administration of desmoteplase leads to transitory derangement of fibrinogen, D-dimer, alpha2-antiplasmin, and plasmin and antiplasmin complex which normalize within 4–12 h. It does not alter a prothrombin test, international normalized ratio, activated partial thromboplastin time, and prothrombin fragment 1.2. Desmoteplase was tested in myocardial infarction and pulmonary embolism and showed promising results versus alteplase. In ischemic stroke trials, desmoteplase was linked to increased rates of symptomatic intracranial hemorrhages and case fatality. However, data from “The desmoteplase in Acute Ischemic Stroke” Trials, DIAS-3 and DIAS-J, suggest that the drug is well tolerated and its safety profile is comparable to placebo. Desmoteplase is theoretically a superior thrombolytic because of high fibrin specificity, no activation of beta-amyloid, and lack of neurotoxicity. It was associated with better outcomes in patients with significant stenosis or occlusion of a proximal precerebral vessels. However, DIAS-4 was stopped as it might have not reached its primary endpoint. Due to its promising properties, desmoteplase may be added into treatment of ischemic stroke with extension of the time window and special emphasis on patients presenting outside the 4.5-h thrombolysis window, with wake-up strokes and strokes of unknown onset.

1 Introduction

1.1 Acute Ischemic Stroke and Therapeutic Window

Stroke is the second leading cause of mortality and morbidity, with one in six deaths from cardiovascular disease being due to all types of strokes in 2018 [1]. Moreover, every 40 sec, a stroke is declared in the United States (US) and, every 4 min, a stroke-related death is documented in the US with a yearly count of more than 795,000 stroke cases. Approximately 610,000 cases of these are new-onset stroke cases, and an average of 185,000 (1 in 4) cases occur in people with a previous history of stroke [2]. Strokes affect 50% of survivors with a high rate of serious long-term disabilities worldwide [3] and represent a daily serious socio-economic
burden in both developed and developing countries, with US$46 billion stroke-attributed costs in the US between 2014 and 2015, including the cost of health care services, stroke treatment, and work absenteeism [2, 4]. Furthermore, ischemic strokes represent 87% of all stroke etiologies, leading to brain function loss and to a large extent of different pathophysiological manifestations secondary to cerebral ischemia [2]. Most stroke-related disabilities are largely due to late-stage diagnosis [5, 6], as well as to costly medication with limited availability, and the narrow therapeutic window. In fact, there is currently only one agent approved for the treatment of acute ischemic stroke within the first 4.5 h after onset: alteplase (recombinant tissue plasminogen activator; rtPA) [7, 8].

Intra-arterial (IA) or intravenous (IV) administration of different thrombotic agents, such as streptokinase, urokinase, and recombinant urokinase have been studied without any satisfactory results [9]. Furthermore, neurologic and radiologic outcomes with IV tenecteplase were similar to those with alteplase when the drugs were administered within 4.5 h after symptom onset in patients with acute ischemic stroke [10].

Nonetheless, recent studies, such as the Prolyse in Acute Cerebral Thromboembolism (PROACT) study, reported an improved clinical outcome at 90 days of treatment with IA recombinant prourokinase administration, within 6 h of the onset of acute ischemic stroke [11]. Moreover, Alison et al. [12] reported a probability of tenecteplase to be superior to rtPA for large vessel reperfusion in patients with salvageable penumbra. Similar results were reported by Fana et al. [13], showing that tenecteplase may increase the rate of reperfusion in comparison with rtPA, prior to endovascular thrombectomy in patients with basilar artery occlusion. However, the reported findings still need to be translated into improved clinical outcomes. Furthermore, due to real-life difficulties in stroke patients reaching the hospital in time, including out-of-hospital and in-hospital delays, thrombolysis with alteplase may not be possible in all patients within the 4.5-h time window [14, 15]. The impact of the extension of the thrombolysis time window from 3 to 4.5 h, using data from the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry and the third European Cooperative Acute Stroke Study, was very significant [15, 16].

Moreover, according to Maestroni et al., the average delay from stroke onset to hospital arrival is 5.4 h (interquartile range 2.7–11.6); 28% of patients arrive within 3 h and 53% within 6 h post-stroke onset [17]. Recently, a significant increase in the mean interval between the ‘last-known-well’ timepoint (LKW) and the time of presentation of a stroke patient to the hospital was attributed to the current COVID19 pandemic. In fact, public measures to limit the spread of COVID-19, such as the worldwide imposed social distancing, telemedicine facilitation, or shelter-in-place orders, as well as stay-at-home policies, have had unwanted repercussions on proper on-time reactions to a stroke onset, and have increased delayed care and detrimental outcomes [18].

The same study has reported a significant 160-min average increase \( P < 0.03 \) in mean LKW-presentation interval between March 2020, a period of COVID-19 (603 ± 1035 min), when compared to 2 months (February–March 2019) of no COVID-19 baseline period (442 ± 435 min) [18].

Moreover, a future additional re-emergence of COVID-19 or resurrection of other pandemic outbreaks could occur and affect the ability to seek medical help shortly after symptoms onset, and are reasons to point to the limitation related to the use of alteplase. However, currently available alternatives to alteplase are still limited to endovascular reperfusion therapy, such as mechanical embolotomy [19]. Nevertheless, this kind of stroke management entails high costs and requires developed facilities and highly skilled professionals [20, 21]. Thus, pharmacological procedures with wider times windows (above 4.5 h), replacing mechanical ones, require further investigation.

In this review, we highlight, discuss, and summarize the potential of desmoteplase as a promising pharmacological intervention which, in resource-limited contexts, as well as when other pharmacological thrombolysis is contraindicated, or might be ineffective, can commonly be used as an alternative therapy in acute ischemic stroke. In December 2014, Lundbeck discontinued the development of desmoteplase in acute ischemic stroke due to insufficient clarity regarding the enrolment of patients in future prospective trials [22]. However, the study of desmoteplase pharmacodynamics has recently regained much more interest, and clinical and translational studies are taking place in order to decipher the unknown about the dose versus effect of desmoteplase as a thrombolytic agent in stroke patients.

A literature review was conducted following simple search strategies to identify peer-reviewed literature (e.g., peer-reviewed articles, database-specific filters) by relative search terms as well as Boolean logic used to combine search terms. Three databases (PubMed®, CINAHL, and Cochrane) were used for the search.

These databases were identified because they represented comprehensive repositories of citations, abstracts, and relevant full articles.

Moreover, hospital databases have also been explored to access some useful tools, such as Lexicomp, Micromedex, and other drug information portals, providing evidence-based referential drug information. The latest literature search was performed in August 2021.
1.2 Development of Desmoteplase

1.2.1 Discovery and Structure

With the silver jubilee of alteplase as the unique thrombolytic agent, Reed et al. [23] outlined the indications, contraindications, activity, adverse events, and toxicity associated with rtPA therapy. In fact, the adverse event profile and potential for toxicity, such as neurotoxicity and increased bleeding risks, as well as its only 5-min half-life [23–25], have encouraged efforts over the past 25 years to discover new pharmacological therapies, such as new modified tissue plasminogen activators. An exhaustive list of those contains reteplase, tenecteplase, desmoteplase, monteplase, pamiteplase, lanoteplase, and alfimeprase [26, 27]. Of this list, tenecteplase and desmoteplase have proved promising treatment potentials with increased safety and efficacy at 24 h and 90 days.

In fact, both agents have shown increased plasma half-lives and fibrin specificity, improved resistance to plasminogen activator inhibitors, and almost no neurotoxicity [28]. Tenecteplase allows better reperfusion and recanalization [29], as well as an expansion of the treatment window to 6 h. Phase 2 and phase 3 trial confirmations have been obtained for tenecteplase [30, 31]. Desmoteplase is another thrombolytic agent which underwent active phase III research to meet the requirements of an extended time window up to 9 h from stroke onset. The discovery of desmoteplase came from the observation of vampire bats (Desmodus rotundus) needing uninhibited blood flow to satisfy their hunger, which is achieved by hemostatic modulators in their saliva.

This was investigated in the late 1990s by Gardell, who found that bat-derived salivary plasminogen activator was homologous to human tissue plasminogen activator (rtPA) [32, 33]. A complete DNA coding of four plasminogen activators present in the saliva of the vampire bat was achieved by 1991. Three desmoteplase species have been isolated, and these molecules were found to be as effective as rtPA in activating plasminogen in the presence of fibrin [34]. The desmoteplase family (α1, α2, β, γ), relatively smaller fibrinolytic agents, are structurally similar to urokinase plasminogen activator (uPA) and rtPA. The common modules of the desmoteplase family include epidermal growth factor (E), finger (F), kringle (K), and protease (P). These modules yield four distinct isoenzymes with the following distinctive phenotypes: FEKP for desmoteplase α1 and α2, EKP for desmoteplase β, and KP for desmoteplase γ [35].

The amino acid sequence among these four isoenzymes is very similar, with 88.7–99.5% identity despite phenotypic differences [36].

Interestingly, the amino acid sequence of rtPA is closely related to desmoteplase α1 (72.3%) and desmoteplase α2 (74.2%). Unlike rtPA, all four DSPA isoenzymes contain just one lysine-binding kringle 2 K domain (two domains in rtPA) [35]. Desmoteplase α1 and α2 isoforms differ in amino acid substitutions by 11%, mainly in the F, E, and K domains. Desmoteplase β and γ are similar to desmoteplase α2 but have 2 and 13 amino acid exchanges (β and γ, respectively) [37, 38]. The chemical and configurational aspects of rtPA and desmoteplase are shown in Figs. 1 and 2.

1.2.2 Desmoteplase versus rtPA

Of the four desmoteplase isoenzymes, only α1 and α2 bind to fibrin. In contrast to rtPA, the N-terminal region plasmin-sensitive activation site is absent on all desmoteplase isoenzymes, which is why they activate plasminogen as single chain molecules. This latter property renders desmoteplase administration safe from any negative effect on the blood–brain barrier. Moreover, the desmoteplase half-life is of about 4 h compared to 5 min for rtPA [40]. The unique feature of desmoteplase isoenzymes when compared to rtPA is their requirement for a fibrin cofactor. Two desmoteplase isoforms, namely α1 and α2, have demonstrated at least comparable, if not superior, thrombolytic activity, lower fibrinogen degradation, and α2-antiplasmin use when compared to rtPA. In a study by Bringmann et al. [36], the addition of fibrin increased the catalytic efficiency of desmoteplase α1 100,000-fold, which was almost 2000 times more when compared with rtPA.

The ratio of catalytic efficiencies in the presence of fibrin compared to those in the presence of fibrinogen was 12,900 for desmoteplase α1, 6550 for α2, 235 for β, and 90 for γ; this ratio was of 72 for rtPA. This finding has already pointed toward very high fibrin specificity of desmoteplase isoenzymes [35]. A peer-reviewed literature search led by Piekowsk-Jozwiak and Bogoousslavy [37] about the use of desmoteplase in the treatment of ischemia reported a 50,000-fold increase in vitro desmoteplase α1 activity in the presence of fibrin in comparison to a 100-fold enhancement for rtPA. Similar results were previously reported by Schleuning et al. [38].

Recently, Elmira et al. [42] reported new thrombolytic drugs with engineered properties aiming, specially, to enhance fibrin affinity and specificity and to increase half-life. In this study, protein engineering and cutting-edge theoretical methods allowed the design of three-dimensional structures of wild-type reteplase based on homology modeling. The newly developed structures contained the finger domain of desmoteplase as a high fibrin-specific domain. This design aimed to achieve enhanced fibrin affinity and other potential properties, such as decreased neurotoxicity and increased resistance to plasminogen activator inhibitor-1. Experimental assessment showed a 1.9-fold increase in fibrin binding ability, as well as appropriate enzymatic activities in both chemiceral reteplase...
compared to wild-type [41]. Here again, desmoteplase showed a promising alternative for future production of effective thrombolytics with very low neurotoxic activity. Moreover, in an animal model of NMDA-induced injury of basal ganglia, administration of desmoteplase α1 did not induce an excitotoxic effect and neuronal death, which was the case after the administration of alteplase [37, 40, 42, 43].

In addition, the desmoteplase α1 isoenzyme has some more favorable properties over rtPA. The latter crosses the blood–brain barrier via a receptor-mediated process through low-density lipoprotein receptor-related protein (LRP)-dependent transcytosis.

Tissue plasminogen activator can cause blood–brain barrier leakage and led to the passage of rtPA into brain parenchyma under metabolic deprivation in an animal stroke model. The blood–brain barrier passage of desmoteplase α1 is also based on a LPR-mediated route. Thus, desmoteplase α1 antagonizes the neurotoxicity induced by vascular rtPA by competing at the LPR binding site [43].

2 Pharmacokinetics of Desmoteplase

In a phase I trial, Larsen et al. studied the pharmacokinetics of IV desmoteplase in healthy Caucasian and Japanese men [44].

At screening, all the patients had brain MRI, blood pressure assessment, and ECG. The single ascending dose study design included two different cohorts of participants: a first cohort of Caucasian men, randomized to receive IV desmoteplase 50 μg/kg injection (n = 6) or placebo (n = 3), and
a second one of Japanese men randomized per dosage group of IV desmoteplase 50 μg/kg (n = 6), 70 μg/kg (n = 6), and 90 μg/kg (n = 6) or placebo (n = 3). For both cohorts, each desmoteplase dose was increased after assessing the safety and tolerability of the previous dose. Pharmacokinetic parameters were found to be similar in both Japanese and Caucasian men after a single IV dose of 50 μg/kg desmoteplase, although a 13% difference of the AUC between the Caucasian versus Japanese subjects needs to be noticed. The pharmacokinetics data are detailed in Fig. 3.

Recently, a Russian review mentioned desmoteplase as one of the latest modified variants of a tissue plasminogen activator with a prolonged clearance time, high fibrin-selectivity, and bolus delivery, to be used in acute ischemic stroke treatment [45]. Moreover, Deborah et al. [46] tested the corneal and scleral permeability of desmoteplase ex vivo both in different animal species and in humans. The rationale behind this study was mainly the documented failure of rtPA to reach fibrinolytic concentrations that are capable of resolving intraocular fibrin. The authors’ choice of desmoteplase relied on its structural similarity to rtPA, but its smaller molecular weight as a fibrinolytic agent with a higher fibrin selectivity, longer half-life, and especially its higher biocompatibility. Results of this study have reported a higher ability of desmoteplase to permeate both cornea and sclera ex vivo in all the species tested, ranging, respectively, from 0.0 to 16.3 μg/mL and 0.0 to 11.4 μg/mL in rabbits, 0.3 to 5.6 μg/mL and 3.1 to 9.2 μg/mL dogs, 2.1 to 14.9 μg/mL and 4 to 8.7 μg/mL in horses, and 0.6 to 3 μg/mL and 2.9 to 18.1 μg/mL in pigs. Preserved human corneas showed concentrations ranging from 0.07 to 12.9 μg/mL of desmoteplase after diffusion through tissue culture, suggesting that in vivo permeability may be possible [46].

3 Clinical Pharmacodynamics of Desmoteplase

The pharmacodynamics of desmoteplase were also studied by Larsen et al. [44], who found that coagulation markers demonstrated similar responses in Caucasian and Japanese subjects following an IV 50 μg/kg dose. In comparison with placebo, there were no apparent changes of prothrombin time, international normalized ratio, activated partial thromboplastin time, and prothrombin fragment 1.2 following injection of any dose of desmoteplase. There was a dip of plasma fibrinogen levels from 2.5 g/L (range 1.96–3.53) to 1.6 g/L (1.03–2.42) observed 5 min after administration. Normalization was seen between 2 and 4 h, even with the highest dose of 90 μg/kg.

The plasma level of alpha2-antiplasmin dropped from 101% (97–106%) to 73% (68–89%) at 5 min after dose administration and normalized after 1 h (90 μg/kg dose). Plasma plasminogen levels dropped from 97 g/L (87–111 g/L) to 78 g/L (60–96 g/L) 5 min post-administration and normalized at 2–4 h (90 μg/kg dose). There was a dose-related increase of D-dimer from a variable baseline (21–274 μg/L): the maximum mean increases up

Fig. 2 Schematic of desmoteplase (DSPA) α, β and γ compared with tissue plasminogen activator (t-PA). Structural domains: F finger domain, EGFD epidermal growth factor domain, K kringle domain, PD protease domain
to 4 h post-dose were 14-fold (287–6423 µg/L) for 50 µg/kg, 26-fold (145–6426 µg/L) for 70 µg/kg, and 47-fold (147–11011 µg/L) for 90 µg/kg doses. The plasma plasmin–antiplasmin complex levels showed a dose-related increase from baseline (234–298 µg/L) of approximately six-fold (1198–1987 µg/L) for 50 µg/kg, seven-fold (2012–3738 µg/L) for 70 µg/kg, and eight-fold (2156–3994 µg/L) for 90 µg/kg IV doses at 5 min post-administration. All these values normalized at 12 h. A strong correlation between plasma fibrinolytic activity and plasma concentration of desmoteplase was reported at all doses in both the ethnic groups studied (Pearson correlation range between 0.813 and 0.978). Overall, desmoteplase was safe and well tolerated; only two subjects had adverse events probably related to desmoteplase, consisting of a mild headache and hematoma [44].

Pharmacokinetics and pharmacodynamics of desmoteplase with other well-known thrombolytic agents are compared in Table 1, showing a longer half-life of desmoteplase and a slower clearance, both in line with bolus administration of this medication. Table 1 also shows differences in fibrin selectivity and plasminogen activator inhibitor effects between these agents.

### 4 Clinical Efficacy and Safety

Desmoteplase was studied in different clinical indications such as myocardial infarction, pulmonary embolism, and ischemic stroke [37].

#### 4.1 Results of Clinical Trials

One open-label phase II clinical study in 26 patients assessed the efficacy, safety, and tolerability of IV (bolus of 0.5 or 0.75 mg/kg) desmoteplase α1 for thrombolysis after acute
myocardial infarction. The rate of recanalization achieved was 65% [47].

Another phase II study compared the thrombolytic efficacy and safety of desmoteplase IV administration (125, 180, and 250 μg/kg) with alteplase (100 mg) in 34 patients with pulmonary embolism. This study showed that desmoteplase at doses of 180 and 250 μg/kg had similar or greater efficacy compared with alteplase 100 mg, with a faster onset of action and comparable safety [50]. Moreover, the current license of alteplase allows for a 4.5-h time window. However, there is a significant unmet demand for effective thrombolytic treatment for both patients presenting out of the current alteplase time window, including wake-up patients with unknown time of onset, and patients with known time of onset but above 4.5–6 h (Fig. 4) [37, 51].

On the other hand, desmoteplase treatment allows a longer therapeutic window (> 4.5 H) for stroke patients with no safety concerns. Desmoteplase in the Acute Ischemic Stroke Trial (DIAS) was a phase II, dose-finding, placebo-controlled, double-blind, dose-ranging study in patients with acute ischemic stroke and MRI perfusion/diffusion mismatch. Patients were treated with IV desmoteplase 90 μg/kg, 125 μg/kg, or placebo within a 3- to 9-h time window. The primary endpoint was 90-day outcome and 186 patients received the treatment. Good clinical outcome was found in 47% of patients treated with 90 μg/kg, 36% with 125 μg/kg, and 46% with placebo. Rates of sICH were of 3.5%, 4.5%, and 0%, and case fatality rates were 11%, 21%, and 6%, respectively. The overall results of this study did not show any benefit with desmoteplase [54].

The trial investigators attributed this lack of benefit to an inadequate sample size and inconsistencies in mismatch assessments. Additionally, DIAS-2 was based on a lower risk population than the previous desmoteplase trials; this probably resulted in a higher proportion of response rates in the placebo group (46% vs. 22% in DIAS and 25% in DEDAS) [37, 51, 54]. DIAS-3 and DIAS-4 were two placebo-controlled, double-blind safety/efficacy trials testing a single IV bolus of desmoteplase at 90 μg/kg within a 3- to 9-h time window in patients with proximal cerebral artery occlusion or high-grade stenosis. The primary outcome was modified Rankin Scale (mRS) score 0–2 at 90-days [37]. DIAS-3 enrolled 492 patients (247 assigned to desmoteplase, and 245 to placebo).

No difference in primary outcome as mRS score 0–2 at day 90 between 121 (51%) patients in the desmoteplase group and 118 (50%) patients in the placebo group (adjusted OR 1.20, 95% CI 0.79–1.81, p = 0.40) [57]. However, significant difference in outcomes measured with mRS in patients with small ischemic injury favored desmoteplase over rt-PA (OR 2.59; 95% CI 1.21–5.51; p = 0.0139). Interestingly, patients treated over 7 h from onset had better outcomes (OR 1.59; 95% CI 1.00–2.53; p = 0.0494). There was no difference in case fatality (10% in both groups), serious adverse events (27% vs. 29%),

### Table 1 Comparison of pharmacokinetics and pharmacodynamics of selected thrombolytics [48, 49]

| Thrombolitic | Mol. weight (kD) | t½ (min) | Clearance ml/min | Elimination | Fibrin selectivity | PAI-1 inhibition |
|--------------|-----------------|----------|-----------------|-------------|-------------------|-----------------|
| Urokinase    | 32/54           | 2        | 179 ± 55        | Liver       | –                 | +++             |
| rtPA         | 68              | 5        | 550–680         | Liver       | ++                | +++             |
| Tenecteplase | 65              | 25       | 119 ± 49        | Liver       | +++               | –               |
| Desmoteplase | 52              | 168      | 168.3           | Liver       | ++++++            | ?               |

- Clearance: 2 ml/min/kg
- Elimination: Liver
- Fibrin selectivity: +++
- PAI-1 inhibition: question mark

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### Endnotes:

[47]Age of onset was a new factor in 65% of cases.

[50]The trial investigators attributed this lack of benefit to an inadequate sample size and inconsistencies in mismatch assessments.

[54]DIAS-2 was a randomized, placebo-controlled, double-blind, dose-ranging phase III study in patients with acute ischemic stroke and MRI perfusion/diffusion mismatch.

[57]There was no difference in case fatality (10% in both groups), serious adverse events (27% vs. 29%).

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frequency of sICH (3% vs. 2%), symptomatic cerebral oedema (2% vs. 2%), or major hemorrhage (4% vs. 6%) in the two groups, respectively. This study showed that desmoteplase was safe, but that it did not improve functional outcomes when given to patients with ischemic stroke and major cerebral artery occlusion between 3 and 9 h of symptom onset [57].

The recruitment into DIAS4 has been stopped as the result of DIAS3 indicated that the study was unlikely to reach its primary endpoint with the current protocol [56]. DIAS-J (Clinical Study of Desmoteplase in Japanese Patients with Acute Ischemic Stroke) followed the DIAS-3 and DIAS-4 studies. It evaluated safety and tolerability of IV desmoteplase at two doses (70 μg/kg and 90 μg/kg) versus placebo administered from 3 to 9 h of acute ischemic stroke in a Japanese population. The primary endpoint was the presence of sICH within 72 h post-treatment, observed in two patients treated with placebo and in one patient intravenously treated with 70 μg/kg of desmoteplase. The rates of any sICH were 43.8% in patients treated with placebo, 50% in 70 μg/kg desmoteplase, and 56.3% in 90 μg/kg desmoteplase groups. Overall, IV desmoteplase at both 70 and 90 μg/kg doses had a favorable safety profile and was well tolerated in Japanese patients with acute ischemic stroke when administered 3–9 h after stroke symptoms onset [58].

4.2 Results of Systematic Reviews and Meta-Analysis

In a post hoc analysis, Fiebach et al. grouped patients from DIAS, DEDAS, and DIAS-2 according to Thrombolysis in Myocardial Infarction (TIMI) vessel status. The results showed that, in DIAS-2, 70% of patients had normal flow or low-grade stenosis as per the TIMI criteria (TIMI 2-3), and that a majority of them had a favorable outcome. Moreover,
patients with vessel occlusion or high-grade stenosis (TIMI 0–1) showed a favorable outcome in 18% of placebo-treated patients and in 36% and 27% of those treated with IV desmoteplase at 90 μg/kg and 125 μg/kg, respectively. A pooled analysis reported an OR of 4.144 (95% CI 1.40–2.23; p = 0.01) favoring desmoteplase over placebo; no effect of the medication was shown in patients without significant stenosis (OR 1.109). These results point toward the efficacy of desmoteplase in patients with mismatch and proximal vessel occlusion or severe stenosis [59].

Additionally, a systematic review and meta-analysis by Li et al in 2017, pooled data from the 6 different randomized clinical trials (RCTs) (DIAS 2001, DEDAS 2003, DIAS-2 2005, DIAS-3 2009, DIAS-J 2010, and DIAS-4 2014) on IV desmoteplase treatment of acute ischemic stroke patients within 3–9 h after symptom onset. This analysis has been conducted in order to evaluate asymptomatic intracerebral hemorrhage, good clinical outcome at 90 days, reperfusion 4–8 h post-treatment, and symptomatic intracerebral hemorrhage and death rates for respective measurements of desmoteplase’s efficacy and safety. Altogether, the above described six trials reported data on a total of 1071 patients who received desmoteplase as a thrombolysis treatment at 3 h post-onset. The results of all doses combined have shown that desmoteplase was associated with increased reperfusion (OR 1.57; 95% CI, 1.10–2.24; p = 0.01 vs. control). In addition, the results of subgroup analysis showed that desmoteplase 90 μg/kg (OR 1.53; 95% CI 1.07–2.21; p = 0.02 vs. control) and 125 μg/kg (OR 4.07; 95% CI 1.16–14.24; p = 0.03 vs. control) were associated with an increase in reperfusion with a tendency to increase asymptomatic intracerebral hemorrhage (OR 1.25; 95% CI 0.97–1.62; p = 0.09 vs. control). However, no increase sICH and death rate were noted with desmoteplase and the difference in the clinical response at 90 days (OR 1.14; 95% CI 0.88–1.49; p = 0.31 vs. control) was not significant [60]. On the other hand, a second systematic review and meta-analysis of five pooled RCTs performed by Elmaraezy et al. on a total of 821 patients was in accordance with the first one, and favored desmoteplase over placebo in terms of reperfusion 4–24 h post-treatment (OR 1.49, 95% CI 1.02, 2.19). However, the same study failed to confirm the efficacy endpoint at 90 days (OR 1.16, 95% CI 0.86, 1.55) and to report significant differences in primary safety outcomes (sICH: OR 1.29, 95% CI 0.53, 3.16, and mortality within 90 days: OR 1.20, 95% CI 0.73, 1.97). The discrepancy between the two studies can be attributed to different factors, such as different pooled effect size, and, more importantly, to the study design, such as differences in inclusion and exclusion criteria [61].

Nevertheless, a meta-analysis by Grant et al. [62] aimed to relate baseline angiography features in acute ischemic patients with the accurate prediction of later response to IV thrombolytics in ischemic stroke. Therefore, angiograms from the IST-3 (Third International Stroke Trial) were analyzed, and angiography findings were compared and tested for interactions with alteplase and desmoteplase. Moreover, all available angiography data from other RCTs on IV thrombolytics were also meta-analyzed; 2 trials on IV alteplase (288 patients from IST-3 and 87 from the Echoplanar Imaging Thrombolytic Evaluation Trial) and 3 trials on IV desmoteplase (216 patients from DIAS, DIAS-2, and DEDAS) were included. Findings of this study have shown no significant interaction between angiography findings and alteplase effect on the Oxford Handicap Scale (p ≥ 0.075) in IST-3.

However, meta-analysis of five trials of alteplase or desmoteplase, including the IST-3 trial, showed the advantageous effect of thrombolytics on the study primary outcome (OR > 1) in patients with arterial obstruction (OR 2.07; 95% CI 1.18–3.64; p = 0.011) versus those without arterial obstruction (OR 0.88; 95% CI 0.58–1.35; p = 0.566) (p for interaction 0.017) [62].

Consequently, it is plausible to speculate that there may still be a benefit from desmoteplase in late-treated patients selected by MRI with small ischemic lesions when compared with rtPA-treated patients. This may require further studies in the subpopulation of patients not covered by the current rt-PA licensing, such as wake-up strokes or strokes beyond the 4.5- to 6-h window.

5 Conclusions

It is important to note that, in light of the recent progress that has been made and the ongoing development of thrombolytic drugs, desmoteplase has been largely reported as a safe and well-tolerated alternative in stroke subjects.

Plasma fibrinolytic activity is linearly related to its blood concentration. Administration of desmoteplase leads to transitory derangement of clotting parameters which normalize within 4–12 h. Desmoteplase was tested in myocardial infarction and pulmonary embolism, and showed promising results versus alteplase.

In ischemic stroke trials, desmoteplase was linked to increased rates of symptomatic intracranial hemorrhages (including fatal ones) and case fatality, but no clear relationship to the dose of the medication was identified. The post hoc analyses point toward a benefit of this medication in patients with a mismatch and proximal stenosis or occlusion. Data from most recent studies led to the termination of further clinical development of this compound in acute ischemic stroke. The story of desmoteplase reiterates a frequent phenomenon in this indication. Due to its promising properties, desmoteplase may add to treatment of ischemia with an extension of the time window, with a special...
emphasis on patients presenting outside the 4.5-h thrombolysis window with wake-up strokes and strokes of unknown onset. In addition, the recent rise of interventional thrombolysis as routine practice is changing the whole landscape of the management of acute ischemic stroke. No matter the developments in other areas of stroke care, one needs to consider the lack of direct transposition of theoretical models and basic science into clinical effectiveness. Thus, considering that thrombolytic therapy is sometimes accompanied by harmful hemorrhagic insults, it is very important for a window of time to be established wherein therapy can safely be performed. More basic and clinical studies have to be developed to come up with next-generation thrombolytics.

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