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Intravenous thrombolysis for acute ischemic stroke: From alteplase to tenecteplase

Nan Yang, Hangil Lee[1], Chuanjie Wu

Abstract:

Stroke is one of the primary causes of morbidity and death worldwide. While intravenous (IV) thrombolysis with alteplase has been widely proven to be beneficial for acute ischemic stroke patients, it still has many limitations. Tenecteplase, a revised version of alteplase, is a potential alternative IV thrombolytic agent that has benefits over alteplase. The aim of this mini-review is to summarize the advancements in IV thrombolysis for severe ischemic stroke, specifically the development and transition from alteplase to tenecteplase.

Keywords:

Alteplase, stroke, tenecteplase

The intravenous (IV) thrombolysis combined with alteplase has been proven beneficial for people suffering from acute ischemic stroke. However, despite this extension of the time window, the rate of disability among survivors remains at a staggering 50%.[1] Most patients with stroke arrive at hospitals too late or are ineligible for alteplase therapy for various reasons. As a modified version of alteplase, tenecteplase can be given as a unitary bolus without requiring a device, offering practical clinical advantages over alteplase. Various doses of tenecteplase have been recommended for different types of strokes based on the instruction published by the American Heart Association/the American Stroke Association[2] in 2019, patients who will undergo systematic thrombectomy with no contraindications to IV fibrinolysis are advised for taking tenecteplase (maximum 25 mg, unitary bolus of 0.25 mg/kg), considering the evidence is weak and low quality. Based on the systematic review and meta-analysis of eight trials (six randomized controlled trials [RCTs] and two observational trials)[3] involving 2031 patients who had acute ischemic stroke, tenecteplase had a significant positive effect on recanalization rates and functional outcomes for 3 months. It has also been shown that the IV thrombolytic did not differ significantly in intracranial bleeding risk compared to alteplase.

Dose of Tenecteplase

However, the ideal dose of tenecteplase is still a matter of debate. It has been observed in several types of research[4,5] that tenecteplase at dosages of 0.25 mg/kg or 0.4 mg/kg is more effective than 0.1 mg/kg in patients with strokes. Tenecteplase at 0.4 mg/kg was shown as safe and effective as alteplase in the NOR-TEST study performed in 2017.[6] Since most patients included in this study suffered from mimics or mild strokes, it was difficult to detect a significant difference. In response, NOR-TEST 2 was designed to include patients with mild-to-severe ischemic stroke,[7] which found that 0.4 mg/kg tenecteplase was linked to higher rates

Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China, [1]Department of Neurosurgery, Wayne State University School of Medicine, Detroit, MI, USA

Address for correspondence:
Dr. Chuanjie Wu, Department of Neurology, Xuanwu Hospital Capital Medical University, Beijing 100053, China.
E-mail: wuchuanjie@xwhosp.org

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of symptomatic intracerebral hemorrhage, mortality, and disability in comparison to 0.9 mg/kg alteplase, suggesting that 0.4 mg/kg tenecteplase had worse functional consequences compared to alteplase. In conclusion, this study concluded that tenecteplase at 0.4 mg/kg is inferior to alteplase in the management of moderate and severe ischemic strokes. Thus probably, 0.25 mg/kg tenecteplase might be an alternative dosage among persons with ischemic stroke.

To determine the optimal dosage of tenecteplase in patients suffering from ischemic stroke, the EXTEND-IA TNK trial performed a head-to-head comparison of 0.4 mg/kg versus 0.25 mg/kg dosages of tenecteplase.[8] They found no advantages to 0.4 mg/kg tenecteplase compared with 0.25 mg/kg in ischemic stroke patients.

Tenecteplase versus Alteplase

A recent study of 1600 participants[9] found tenecteplase 0.25 mg/kg is comparable to alteplase 0.9 mg/kg respective to functional, quality of life, and safety outcomes for acute ischemic stroke patients. Recently, a meta-analysis of nonrandomized data comparing tenecteplase with alteplase reported that neither individual RCT studies nor other meta-analyses have indicated any safety concerns regarding intracranial hemorrhage and mortality of tenecteplase compared to alteplase.[10]

Reperfusion Injury and Tenecteplase

Reperfusion injury has the potential to damage tissues and organs after thrombolysis for stroke patients. Controlled reperfusion reduces hemorrhagic transformation in acute ischemic strokes.[11] As a result of the Australian Tenecteplase versus Alteplase Stroke Thrombolysis Evaluation Trial in the Ambulance study, patients receiving 0.25 mg/kg tenecteplase had significantly reduced computed tomography (CT) perfusion lesion volume after arriving at the hospital compared to those receiving 0.9 mg/kg alteplase. (Of note, tenecteplase was infused with 12 ml bolus, while alteplase required 35 ml).[12] This study suggests that tenecteplase is superior to alteplase in reducing posttherapy reperfusion damage, and conferring better early clinical recovery.

Other Benefits of Tenecteplase

Tenecteplase proved more practical in a prehospital setting because of its time-saving properties. As Tenecteplase does not require an infusion pump, patient handovers are simplified and dosing errors are reduced. Because of these factors, patients receiving tenecteplase had shorter waiting times from CT imaging to initiation of thrombolytic treatment than patients receiving alteplase.

In summary, tenecteplase at 0.25 mg/kg was superior to alteplase in reducing perfusion lesion volumes and in improving clinical outcomes at an early stage. These results support that tenecteplase at a dose of 0.25 mg/kg is a promising alternative to alteplase as the standard-of-care IV thrombolytic agent for acute ischemic stroke patients. However, the findings of some of these trials, such as EXTEND-IA TNK-2, were conducted in a highly selected group, and findings might not be applicable in all circumstances. Only randomized controlled trials will provide sufficient data to support regulatory approval of tenecteplase as a global alternative to alteplase in acute stroke; further research is necessary.

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Conflicts of interest

There are no conflicts of interest.

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