Pharmacological Reperfusion Therapy with Tenecteplase in 7,668 Indian Patients with ST Elevation Myocardial Infarction – A Real World Indian Experience

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Abstract

Objective: This real-world, observational, prescription event monitoring study was conducted to evaluate safety and efficacy of indigenous tenecteplase (TNK-tPA) in Indian patients presenting with ST elevation myocardial infarction (STEMI).

Methods: This is a multi-centric, observational, prescription event monitoring study. Data was collected for 7,668 patients from 1,307 investigator sites across India from January 2011 to February 2016.

Results: Overall, 76.71% patients were hypertensive, 47.97% patients were diabetic, 42.01% had dyslipidemia, 24.35% had ischemic heart disease and 40.82% patients were smokers. The overall rate for achieving clinically successful thrombolysis by TNK was 93.34%. Delayed administration of tenecteplase yielded lower success rate (84.66%) as against those patients who received tenecteplase within 3 hours of symptoms (94.34%). 93.2% patients had chest pain resolution after pharmacological fibrinolysis. Overall 91.1% patients had 50% resolution of ST elevation at 90 minutes and mean time for 50% ST resolution was 72.06 minutes. Overall 53 patients died (mortality of 0.69%) before discharge. The incidence of bleeding (excluding stroke) was 1.77%, any stroke without ICH was 0.18% and any ICH was 0.38%.

Conclusion: The findings of this study further reinforce the safety and efficacy of indigenous TNK-tPA in Indian patients presenting with STEMI, including high-risk sub-groups. The study also highlights the importance of early reperfusion therapy.

Editorial Viewpoint

• Use of tenecteplase in thrombolysis is increasing in India due to its safety and efficacy.
• This study highlights early repurfusion by tenecteplase with its efficacy and safety even in high risk patients.

Introduction

Coronary artery disease (CAD) is one of the most common non-communicable diseases in India and one of its severe complications is ST-elevation myocardial infarction (STEMI). The rate of increase of coronary vascular diseases (CVD) in developing countries is almost double in comparison to developed countries. This especially applies to the younger generation. Reddy et al. reported that about 52% of deaths from CVDs in India occur before 70 years of age, compared with 23% in established-market economies. It is reported in a survey conducted in 45 rural villages in India that 32% of all deaths were due to CVD. It proves that the epidemic has reached its advanced stage even in rural India.
Moreover, as per data presented of Mumbai was 240 minutes. A recent study done by Noorani et al. showed that the median pre-presentation to the hospital with chest pain and diagnosed with acute STEMI was 120 min from first medical contact (FMC) as recommended in the guidelines.

There is a continuing challenge in delivering timely and effective PCI for STEMI. Compelling evidence suggests that delay to PCI is associated with lesser myocardial salvage and worse outcomes, and in such situations, pharmacological approach to reperfusion with fibrinolytic therapy should be considered. Pharmacological fibrinolysis is traditionally well accepted, evidence based, and guideline supported, especially in patients presenting early after symptom onset, that is, within 3 hours. The most preferred current fibrinolytic strategy includes the combination of bolus tenecteplase, aspirin, clopidogrel, and enoxaparin as initial therapy. Molecules available for fibrinolysis are tenecteplase (Grade 1A), reteplase (Grade 1B), alteplase (Grade 1C) or streptokinase (Grade 2B) administered alongside contemporary adjunctive medical therapy (as per API recommendations). Tenecteplase with multiple evidence-based advantages is the best suitable option in Indian STEMI patients in whom PCI cannot be performed most of the time due to logistic reasons.

This study is a continuation of earlier published Indian registry of 15,222 Indian STEMI patients thrombolysed with tenecteplase. The objective of this study was to re-emphasize efficacy and safety of tenecteplase as a fibrinolytic agent in a strategy of prompt fibrinolysis in STEMI patients in India. This article presents the real-world safety and efficacy data for the use of TNK-tPA in Indian patients with STEMI.

### Study Design

This is a multicentric, observational, prescription event monitoring study, designed to evaluate case-records of patients presenting with chest pain and diagnosed with acute STEMI and in whom PCI was not feasible within 120 minutes of a qualifying diagnostic electrocardiogram (ECG) (first medical contact).

### Study population

Data was collected for 7,668 consecutive patients from 1,307 investigator sites across India from January 2011 to February 2016.

### Pharmacological reperfusion

Tenecteplase, (Elaxim) manufactured by Gennova Pharmaceuticals Ltd, Pune, India, was administered to patients of STEMI reporting to the centers, in a weight-adjusted dosing pattern at the discretion of the treating cardiologist/physician as a part of standard clinical practice. Patients also received adjuvant medication as per the physician's instructions.

### Inclusion and exclusion criteria

Participants were eligible for inclusion in the study if they presented to the hospital with chest pain, diagnosed with STEMI by the treating physicians/cardiologists and thrombolysed with TNK as per the discretion of treating physician/cardiologist. Recording of all the parameters mentioned as study data points in the patient health record file was mandatory for inclusion of a patient in the study. Patients with incomplete health record as required by the study protocol, any contraindications for tenecteplase, PCI within the previous month, previous coronary-artery bypass surgery (CABG) were excluded.
Study Endpoints

The safety and efficacy end points are listed in Table 1.

Statistical analysis

We performed a descriptive analysis of the data. Continuous variables are presented in means (standard deviation) or median (inter-quartile range), when skewed in distribution. Categorical variables are presented as proportions. The statistical analysis was performed using SAS software package (version 8.1).

Results

Patients

Data was collected from 1307 centers for 7668 patients treated in between January 2011 to February 2016. Baseline characteristics were as shown in Table 2. Mean chest pain to door time was 116.11±46 minutes. The mean chest pain to door time was less than 3 hours in 76% patients, 3-6 hours in 22% and more than 6 hours in 2% patients.

Concomitant medication

Out of the total patients enrolled, more than 98% received both clopidogrel and aspirin (99.32% and 98.96%, respectively), while 95.62% received unfractionated or low molecular weight heparin. Beta blockers and nitroglycerine were administered in 67.03% and 19.34% patients respectively. Glycoprotein IIb/ IIIa inhibitors (GPI) were administered in 4.13% patients.

Efficacy

The overall rate for achieving clinically successful thrombolysis (CST) by TNK was 93.34% (Figure 1). Delayed administration of tenecteplase (>6 hours from onset of chest pain) yielded lower success rate (84.66%) as against those patients who received tenecteplase within 3 hours of symptoms (94.34%).

93.20% patients had chest pain resolution after pharmacological fibrinolysis with TNK (Figure 2). The mean time to resolution of chest pain was 55.18 ± 8.36 minutes, occurring in <30 minutes in 35% patients. About 91.10% patients had 50% resolution of STE at 90 minutes and mean time for 50% STE resolution was 72.06 ± 3.67 minutes.

In addition, investigator assessed
endpoints were captured. Overall, 99.14% and 98.57% investigators respectively considered TNK as safe and efficacious in the treatment of STEMI. 53 patients died (mortality of 0.69%) before discharge. Reinfarction occurred in 1.5% patients during hospital stay.

**Safety**

There was no procedural complication reported during TNK administration like hypotension. The safety parameters recorded were an overall incidence of bleeding (excluding ICH), the incidence of non-hemorrhagic stroke and ICH. Any bleeding excluding stroke occurred in 1.77% patients, any stroke without ICH in 0.18% and any ICH in 0.38% patients. Angiography was performed in 16.46% patients, while 411 (5.36%) patients underwent PTCA, and 186 (2.43%) had CABG.

**Discussion**

Our study adds to the wealth of evidence from India on real-world use of TNK as a fibrinolytic agent in STEMI patients. CREATE was a large prospective clinical registry of acute coronary syndrome (ACS) patients in 89 large hospital centers across India and Kerala ACS Registry prospectively collected data on 25,748 consecutive ACS admissions from 125 hospitals in Kerala.5,11 In CREATE registry, the median time from symptoms to hospital in STEMI patients was 300 minutes and 38.1% patients reached hospital in less than 4 hours.5 Whereas, in a study by Noorani F et al. in STEMI patients of Mumbai region, the median total pre-hospital delay was 240 minutes.6 In our study, case-scenario was observed to be improved with 76% patients presenting within 3 hours of chest pain.

The Indian Registry by Iyengar et al. analyzed efficacy and safety of tenecteplase in 15,222 patients with STEMI.10 Overall, 95.43% patients had CST, with higher success rate (96.54%) in patients treated within 3 hours than patients presenting more than 6 hours (85.38%), and an overall mortality of 1.69%. Also, STREAM trial demonstrated that patients presenting within 3 hours of symptom onset and fibrinolysed had significantly better outcome (composite of death, shock, congestive heart failure, or re-infarction up to 30 days) than PPCI group.12 Our study also demonstrated the significance of early thrombolysis, wherein most of the patients presented within 3 hours.

In this study, the overall rate for achieving CST by TNK was 93.34%. Similar observation was also made in the ‘Indian Registry’ where more than 90% CST was seen with tenecteplase, including high-risk sub-groups like elderly, diabetics, hypertensives, smokers and hyperlipidemics.10 The fact effectively highlights a satisfactory clinical efficacy of indigenous TNK in routine clinical practice. It has been seen in earlier studies that among patients with an acute myocardial infarction, 10% to 25% have diabetes mellitus.13 In the present study, this prevalence was much higher (48%). Similarly high inclusion rate of diabetic patients was mentioned in a study by Sathymurthy et al. (44.94%).14

ST segment resolution is regarded as a marker of salvaged myocardium by post-thrombolytic reperfusion. Unlike conventional angiography, ST resolution is a useful surrogate indicator of both macro and microvascular perfusion and is therefore especially valuable in evaluating the success of myocardial reperfusion therapy.15 In this study, 91.10% patients had 50% resolution of STE at 90 minutes and time for 50% ST resolution was 72.06 minutes. Coronary pain is an evidence of ongoing ischemia/necrosis, and thus provides an alarm for rescue angioplasty in failed reperfusion.16 In our study, 93.20% patients had chest pain resolution after pharmacological fibrinolysis with TNK.

In-hospital mortality rate was lower (0.69%) compared to the CREATE registry (8.6%) and Kerala ACS registry (8.2%).11 Reasons for differences in outcomes are likely to be driven more by the patient presenting characteristics and early reperfusion than by differences in management, particularly given the similarities in terms of anti-platelet, heparin, beta-blocker, and statin use in all the studies. Being a registry of prescription event monitoring observational study, mortality rate is likely to be underreported.

Danchin N et al. reported mortality rates of 4.3% (3.3% in those receiving thrombolysis pre-hospital and 6.1% in those receiving thrombolysis in-hospital). By contrast, in-hospital mortality was 9.5% in patients who did not undergo reperfusion.17 In our study, mortality rates were less comparatively (0.69%). The overall mortality is lower than earlier reported incidence of 6.18% in the ASSENT-2 and up to 6.5% in TIMI 10B study.13,18 Indian registry reported a total mortality of 1.69%, with over three fold increase in mortality was seen in patients receiving delayed treatment.10 The incidences of bleeding, myocardial re-infarction and heart failure were similar to that reported in TIMI 10B and ASSENT-2 studies. Incidence of bleeding was 1.77% in our study, which is significantly less compared to that reported in the ASSENT-2 trial where-in major bleeding occurred in 4.66% in the tenecteplase group.

**Strengths and limitations**

The main strength of this study is the large sample size and broad coverage of hospitals across geographical regions of India. However, our study has certain limitations. First, the study is observational, uncontrolled, and depends on reported events. Second, data is collected from case records. Further, patient data were gathered from coronary care units due to logistic considerations,
which may have led to an underestimate in event rates, since patients who died in the casualty ward would not have been included in our analyses. Furthermore, post-fibrinolytic angiograms were not available for most of the patients for various reasons and therefore angiography findings were not analyzed.

**Lessons learnt**

This prescription event monitoring observational registry has shown certain strengths and weaknesses of clinical practice in these areas where there are no facilities for PPCI, but fibrinolytic therapy could be administered. Physicians practicing in these centres have exhibited their competence in the management of STEMI and fibrinolytic therapy. There is a substantial scope for improving medical records, and for instituting pharmaco-invasive strategy. The way forward is to know the distances of these centres from nearest PCI capable centres so that these could act as “spoke centres”, should identify and transfer cases to “hubs”, paving path for pharmaco-invasive strategy when PPCI is not possible. The next step of the project is to encourage the setting up of STEMI network in these areas and collect data on reperfusion strategies in STEMI.

**Conclusion**

Pharmacological reperfusion therapy is an evidence-based treatment for STEMI. The findings of this observational study of 7,668 patients in clinical practice further reinforce the safety and efficacy of TNK-rtPA in Indian STEMI patients. Our study also reconfirms the efficacy and safety of tenecteplase in patients with co-morbidities like hypertension, diabetes and dyslipidemia. More importantly, our study reconfirms the importance of early thrombolysis for successful reperfusion rates (and consequently potentially better clinical outcome), especially in the Indian scenario where reaching a PCI center may not be immediately possible. Furthermore, administering thrombolitics proves to be an eminently suitable strategy in the Indian setting, since this study re-establishes the efficacy of a thrombolytic like TNK in prompt and effective reperfusion of the myocardium. Subsequently, the patients could be transferred to PCI centres.

**Conflict of Interest**

The study was supported by Emcure Pharmaceuticals Ltd. The authors are on the advisory panel of Emcure Pharmaceuticals Ltd.

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**References**