Post-Reteplase Evaluation of Clinical Safety & Efficacy in Indian Patients (Precise-In Study)

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Abstract

Background: ST elevated myocardial infarction is a serious and life-threatening condition. In patients suitable for thrombolytic treatment, time is critical and reperfusion should be initiated as soon as possible. Reteplase is commonly used in the management of ST elevated myocardial infarction.

Objective: To assess the safety and efficacy of intravenous Retelex (Reteplase) injection in management of patients with ST elevated myocardial infarction in clinical practice.

Material and methods: An open label, non-comparative, multicentric, post-marketing observational study was conducted in >18 years of patients with ST elevated myocardial infarction (STEMI) receiving Retelex. All patients received 20 units Retelex within 6 hours after the onset of acute myocardial infarction (AMI) symptoms. The dose was given as two 10 unit Intravenous injections each over two minutes 30 minutes apart. Evaluation criteria: Patients were followed on day 1, 3, 5/7 and 30. The primary evaluation criteria was total number of patients showing clinically successful thrombolysis based on 50% resolution of ST-elevation in the maximum affected (adjacent) leads within 90-120 minutes of initiation of Reteplase and resolution of chest pain. Secondary evaluation criteria included percentage of patient requiring rescue percutaneous coronary intervention (PCI), percentage of patient underwent angioplasty or CABG after thrombolysis. Door to needle time was also recorded in patients receiving the study drug. Global assessment of efficacy and safety was done by patient as well as investigator. All adverse events were recorded for safety assessment. Statistical analysis: Mean and percentage were calculated for primary efficacy parameters i.e. 50% resolution of ST elevation and resolution of chest pain. Chi square test was used for comparing the difference between diabetes versus non-diabetes patients for primary efficacy variables as well as for comparing the number of patients requiring rescue PCI, angioplasty and CABG between these two groups.

Results: A total of 228 patients were enrolled out of which 140 were having diabetes mellitus. Out of all patients, 68.9% had ST elevated anterior wall myocardial infarction. Resolution of 50% of ST elevation and resolution of chest pain was reported in 90.50% and 95.4% patients respectively. No significant difference was seen in primary efficacy variables between diabetes versus non-diabetes patients (p=0.1538 for 50% ST elevation resolution, p=0.4031 resolution of chest pain). Rescue PCI was required by 7.6% patients while angioplasty and CABG was done in 22% and 16.8% patients, respectively. No significant difference was seen in diabetes versus non-diabetes patients requiring rescue PCI (p=0.1059), angioplasty (p=0.2172) and CABG (p=0.9128). The incidence of adverse event in this study was 5.3%.

Conclusion: Reteplase IV Injection-recombinant plasminogen activator is effective and well tolerated in the management of ST elevated myocardial infarction (STEMI) in Indian patients including diabetes patients.

Editorial Viewpoint

• Early thrombolysis should be made available to all the patients across India to be administered while transporting patients in ambulance.
• This is an open label, non-comparative post-marketing surveillance.
• There is a definite improvement in therapeutic armamentarium for thrombolysis by addition of Reteplase.
Introduction

Non-communicable diseases are rapidly increasing and mortality due to non-communicable diseases is increasing at a rapid pace. Cardiovascular disease, one of common non-communicable diseases is responsible for high morbidity and mortality all over the world.1 There are about 30 million patients with CHD in India. Coronary heart disease is more prevalent in Indian urban populations. Epidemiological studies have demonstrated the prevalence of CHD in rural adult is less (3-5%) compared to urban (7-10%) adults.2 According to estimates a total of nearly 64 million cases of CVD are likely in the year 2015.3 One of the serious complications of the CAD is ST-elevation myocardial infarction (STEMI), which is a life-threatening clinical emergency.4 Patients with acute coronary syndromes in India have a higher rate of STEMI compared to developed countries.5 ST elevation myocardial infarction (STEMI) can be treated by primary percutaneous coronary intervention (PPCI) and fibrinolysis. Percutaneous coronary intervention if done in timely manner is superior to fibrinolysis.4 However, this may not be possible in many settings because of challenges like time lag in transferring the patient, lack of catheterization facility and limited number of skilled practitioners. In patients suitable for thrombolytic treatment, time is critical and reperfusion should be initiated as soon as possible.4 Despite availability of good treatment, mortality from acute myocardial infarction (AMI) is showing no further reduction due to the pre-hospital phase and in-hospital delays.5 Hence for management of STEMI, immediate administration of a fibrinolytic followed by angiogram and percutaneous intervention (PCI) between 3-24 hours after fibrinolytic therapy may be an attractive option.7 Reteplase is a plasminogen activator which mimics endogenous tissue plasminogen activator (t-PA), a serine protease, converting plasminogen to plasmin and thereby precipitating thrombolysis. It is a third-generation recombinant form of fibrin specific t-PA.6 The half-life of reteplase is longer than that of alteplase; hence it can be used as bolus injection.7 The ease of administration of reteplase because of simple dosage regimen helps for prehospital initiation of thrombolytic treatment in patients with ST-segment elevation myocardial infarction (STEMI). The advantage with this regime is reduction in the time to treatment which is an important factor in improving long-term survival.8

Objective

The objective of the study was to evaluate safety and efficacy of intravenous Retelex (Reteplase) injection in management of patients with ST elevated myocardial infarction in clinical practice

Material and Methods

An open label, non-comparative, multicentric, post-marketing observational study was conducted in adult patients (>18 years of age) with ST elevated myocardial infarction (STEMI) who received Retelex. The decision to administer Retelex (Reteplase) along with other adjuvant drugs was taken solely by the treating physicians as a part of their clinical management. The patients having contraindication to the use of thrombolytic, patients with internal active bleeding or known history of hemorrhagic diathesis or history of previous cardiovascular accident (CVA), transient ischemic attack (TIA) of any kind, intracranial tumor, arteriovenous malformation, cerebral aneurysm, major surgery, parenchymal biopsy, ocular surgery and/or severe traumatism within 6 weeks prior to screening for study were excluded from the study. The patients with unexplained puncture in a non-compressible vascular location in the last 24 hours prior to screening for study and those with confirmed arterial hypertension (>200/110 mm Hg) at entry were also not included in this study. Each patient received a total dose of 20 units Retelex within 6 hours after the onset of acute myocardial infarction (AMI) symptoms. The dose was given as two 10 unit Intraavenous injections each over two minutes, no more than 30 minutes apart. Patients were followed on day 1, 3, 5/7 and 30.

Evaluation criteria: The primary evaluation criteria was total number of patients showing clinically successful thrombolysis based on 50% resolution of ST-elevation in the maximum affected (adjacent) leads within 90-120 minutes of initiation of Reteplase and resolution of chest pain. Secondary evaluation criteria included percentage of patient requiring rescue PCI, percentage of patients who underwent planned angioplasty or coronary artery bypass graft (CABG) after thrombolysis. In addition, door to needle time (ECG diagnosis of STEMI and first dose of Retelex) and concomitant medication were also recorded for patients receiving Reteplase. Repeat ECG was taken within 90 to 120 min after initiation of Retelex (Reteplase). Global assessment of efficacy and safety was done by patient as well as investigator. The efficacy was rated on 4 point (excellent, good, moderate, poor) while safety was rated on 3 points (good, moderate, poor). Safety was assessed through recording all adverse events.

Statistical analysis: Mean and percentage were calculated for primary efficacy parameters i.e. 50% resolution of ST elevation and resolution of chest pain. Chi square test was used for comparing the difference between diabetes versus non-diabetes patients for primary efficacy variables as well as for comparing the number of patients
requiring rescue PCI, angioplasty and CABG between diabetes versus non-diabetes patients. ANOVA was used for evaluating the difference in vital parameters compared to baseline.

Results

A total of 228 patients were enrolled in this study out of which 140 patients had diabetes mellitus. Table 1 shows the baseline characteristics of patients enrolled in the study. The age range of patients was from 27 years to 89 years. Maximum enrolled patients (68.9%) had ST elevated anterior wall myocardial infarction followed by inferior wall and posterior wall myocardial infarction (Table 2).

Efficacy: As shown in Figure 1, 50% resolution of ST elevation (n=221) was seen in 90.50% patients while resolution of chest pain (n=216) was reported in 95.4% patients. No significant difference was seen in number of patients with 50% resolution of ST elevation between diabetes versus non-diabetes patients (p=0.1538 for 50% ST elevation resolution, p=0.4031 resolution of chest pain).

Overall (n=211) only 7.6% patients required rescue PCI while 22% and 16.8% patients underwent angioplasty (n=200) and CABG (n=191), respectively. No significant difference was seen in diabetes versus non-diabetes patients requiring rescue PCI (p=0.1059), angioplasty (p=0.2172) and CABG (p=0.9128).

Global assessment of efficacy: As per the global assessment of

Table 1: Baseline characteristics (n=228)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Mean age (SD)</td>
<td>58.65 (11.69) years</td>
</tr>
<tr>
<td>Male (%)</td>
<td>176 (77.2%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>52 (22.8%)</td>
</tr>
</tbody>
</table>

Table 2: Diagnosis of enrolled patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-elevated anterior wall MI</td>
<td>157 (68.9%)</td>
</tr>
<tr>
<td>ST-elevated inferior wall MI</td>
<td>71 (31.1%)</td>
</tr>
<tr>
<td>ST-elevated posterior wall MI</td>
<td>22 (9.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>37 (16.2%)</td>
</tr>
</tbody>
</table>

Table 3: Mean changes in the vital parameters

<table>
<thead>
<tr>
<th>Duration (days)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>Pulse rate (/min)</th>
<th>Respiratory rate (/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=187</td>
<td>n=186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>147.13 ± 27.84</td>
<td>89.62 ± 17.49</td>
<td>81.88 ± 16.42</td>
<td>22.78 ± 06.67</td>
</tr>
<tr>
<td>3</td>
<td>*133.37 ± 19.05</td>
<td>*83.01 ± 10.86</td>
<td>*76.88 ± 08.39</td>
<td>*20.98 ± 05.15</td>
</tr>
<tr>
<td>5/7</td>
<td>*124.29 ± 12.85</td>
<td>*80.26 ± 09.65</td>
<td>*74.16 ± 07.20</td>
<td>*20.03 ± 04.91</td>
</tr>
<tr>
<td>30</td>
<td>*121.64 ± 11.24</td>
<td>*79.27 ± 06.98</td>
<td>*74.16 ± 06.88</td>
<td>*19.88 ± 04.80</td>
</tr>
</tbody>
</table>

P value: *P < 0.05
efficacy, excellent to good efficacy was reported by 95.6% and 93.8% of patients as evaluated by patients (n=225) and investigators (n=224), respectively (Figure 2).

The most commonly used concomitant medications in the study included aspirin, clopidogrel, LMWH/Heparin and statin (Figure 3). Sorbitrate was used by 9.1% patients.

Effect on vital parameters: As compared to baseline, significant reduction was seen in the vital parameters i.e. blood pressure, pulse rate and in respiratory rate (Table 3). The mean door to needle time was 24.93 (±25.57) minutes in all cases.

Safety assessment: A total of 12 patients (5.3%) patients reported adverse event. Arrhythmia, epistaxis, hematuria, ventricular fibrillation and VT were the adverse events reported in the study. No significant difference was seen in adverse event rate between diabetes versus non-diabetes patients (p>0.05).

Global assessment of tolerability: As per the global assessment of tolerability, good to moderate tolerability was reported by 99% patients as evaluated by patients (n=208) whereas 100% patients reported good to moderate tolerability as evaluated by investigators (n=215), respectively (Figure 4). No significant difference was seen in the tolerability as reported by patients or doctors in diabetes versus non-diabetes patients (p=0.5641 for evaluation by investigator; p=0.8832 for evaluation by patients).

Discussion

Thrombosis is part of the normal physiologic haemostatic response to limit bleeding in case of vascular injury. Usually thrombus remains at the site of injury and does not limit the blood flow. Under some circumstances, the thrombus can occlude the blood vessel. Acute myocardial infarction is one such acute thrombotic occlusive disorder. ST elevated myocardial infarction needs immediate treatment. Thrombolytic treatment should be started as soon as possible to delay the complications. In this study, the door to needle time was less than half an hour i.e. 24.93 minutes.

A fibrin-specific agent has class IA recommendation from the European Society of Cardiology guidelines for the management of STEMI. Reteplase, a plasminogen activator has been well studied in the management of ST elevation myocardial infarction both globally as well as in India. Internationally, in large randomized clinical trials in patients with STEMI, reteplase was found to be superior to alteplase for coronary artery patency at 60 and 90 minutes. Similarly in another study with reteplase, 73.75% patients achieved 50% lowering of ST segment elevation at 6 hours while in our study, 90.5% patients achieved 50% reduction of ST elevation. Similarly large number of patients (95.4%) also had resolution of chest pain. In an Indian observational study with tenecteplase resolution of chest pain was reported in 93.65% patients receiving tenecteplase. In this study, all the patients had received in-hospital tenecteplase as per weight-adjusted dosing. The advantage of Reteplase is its simple dosing schedule i.e. two 10 unit intravenous bolus injections each over two minutes, no more than 30 minutes apart. The bolus injection with reteplase is possible because of its long half-life compared to alteplase. The half-life of reteplase is four times longer than alteplase. Studies in animal have suggested that double bolus regimen is preferable to doubling the single bolus dose of reteplase. The suggested time interval of 30 minutes between two injections is derived from the pharmacokinetic modelling. No statistically different difference was seen clinically successful thrombolysis with tenecteplase in diabetics versus non-diabetics. Similarly, we also did not observe significant difference between diabetes and non-diabetes patients with reteplase. It is also documented in a comparative data that reteplase achieves higher and faster reperfusion after two bolus injections of 10 units than 100 mg infusion of alteplase.

Reteplase was well tolerated by patient in this study. On global assessment of tolerability, none of the patient reported poor tolerability as evaluated by investigators. Thus, proven efficacy and safety finding from this study demonstrates utility of reteplase in Indian patients with STEMI.

Reteplase is a better fibrinolysis agent because of its multiple advantages including lesser amount of drug required to maintain therapeutic level, prolonged half life (13-16 min) and easy administration as no infusion required. The recommended
dosage for reteplase is two IV bolus doses of 10 U over 2 min, 30 min apart. Unlike tenectaplate, the dosing regimen is non-weight-based. The simple dosing regimen has potential to reduce fibrinolytic dosing errors resulting in improved outcome. Reteplase has enhanced thrombolytic and antithrombotic potency due to reversible binding, comparatively low fibrin binding which improves clot penetration and high resistance to inhibition by plasminogen activators. It is less effective in lysing platelet rich plasma clots and aged clots as haemostatic plugs are thought to be older clots that seals small vessel wall injuries.

Conclusion

Reteplase IV Injection recombinant plasminogen activator is effective and well tolerated in the management of ST elevated myocardial infarction (STEMI) in Indian patients including diabetes patients.

Acknowledgement

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References