Clinical Evaluation

Clinical Retrospective and Prospective Evaluation of Efficacy and Safety of Reteplase in STEMI Patients

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Abstract

Reteplase is a third-generation recombinant form of t-PA (tissue plasminogen activator). A phase–III prospective, multi-centric trial and retrospective, post-marketing surveillance (PMS) of reteplase have been conducted to evaluate the efficacy and safety of reteplase in patients with ST segment Elevation Myocardial Infarction (STEMI). Phase-III trial was a prospective, multi-centric, open-label study conducted across 15 centers in India. 80 patients out of 83 screened were enrolled in the study. Patients with STEMI admitted to an intensive care unit in a hospital within 6 hours of onset of symptoms and meeting all eligibility criteria were enrolled in the study. Each patient received a total dose of 20 units of reteplase. The dose was given as two 10 unit intravenous injections each over two minutes, no more than 30 minutes apart. The primary objective of the study was to evaluate the all cause mortality rate at 30 days post-dosing in patients with STEMI following treatment with reteplase. Safety assessment was based on treatment emergent adverse events, physical examinations, vital signs, ECGs, echocardiography and safety laboratory tests. A Post Marketing Surveillance (PMS) following the marketing approval in India was undertaken to assess the safety profile of reteplase in patients with STEMI and/or recent left bundle branch block. Reteplase was administered as two bolus injections of 10 units each. Each bolus was administered as a slow intravenous injection over 2 minutes. Total 204 patients' data has been considered for the analysis in present post-marketing study. The results of both these studies are discussed. In both these studies, reteplase efficacy and safety were well established in treatment of patients with ST segment elevation Myocardial Infarction (STEMI).

Keywords

ST segment elevation Myocardial Infarction (STEMI), Reteplase, Myocardial infarction (MI), arrhythmia, stroke

Introduction

Coronary artery disease (CAD) is currently the most common, non-infectious disease in India and will affect over 65 million people in the country by the year 2015[1]. CAD is a leading cause of death and disability in India and its overall incidence has risen radically over the past two decades. The prevalence rate is also alarming as approximately 3-4% of Indians in rural areas and 8-10% in urban areas have CAD[2]. One of the gravest complications of CAD is ST-elevation myocardial infarction (STEMI), a life-threatening clinical emergency. Since most Indian patients are below poverty line, they are less likely to get evidence-based treatment, and have greater 30-day mortality. Reduction of delays in access to hospital and provision of affordable treatment could reduce this. In patients suitable for thrombolytic treatment, time is critical and reperfusion should be initiated as soon as possible. Despite availability of good treatment, mortality from acute myocardial infarction (AMI) is showing no further reduction

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due to the pre-hospital phase and in-hospital delays[3]. Thrombolysis is almost always delivered to patients after arriving in hospital, losing valuable time.

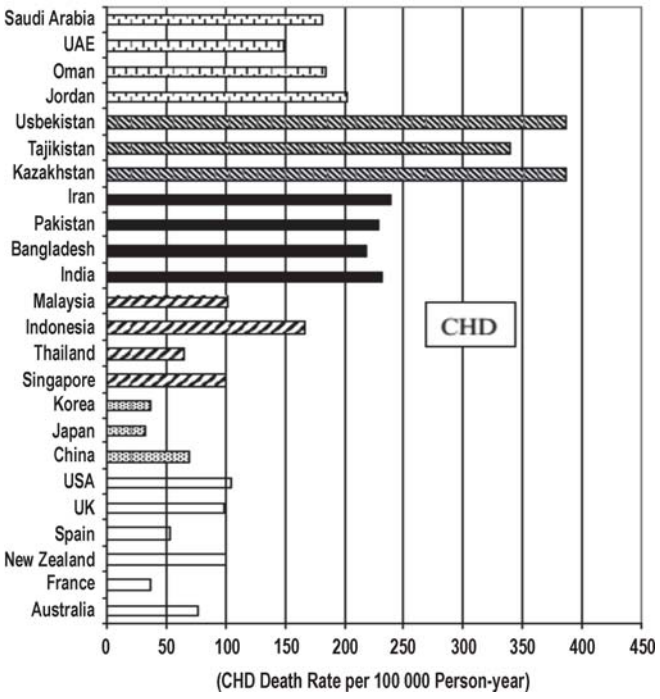


Fig. 1

Age-standardized death rates per 100,000 for CHD across countries in different regions of Asia in 2002. Data from the World Health Organization, Department of Measurement and Health Information. Patterns on the bars represent different regions i.e. Middle Eastern countries and Central Asian countries have different patterns etc.

The available data from the World Health Organization on age-adjusted mortality for men and women combined for CHD are shown in **Fig. 1**[4]. For age-adjusted CHD mortality, it is of interest that East Asian countries have lower mortality than other Asian countries, except Thailand.[5] Other Asian countries have higher CHD mortality than East Asian countries or Western countries. Central Asian countries that belonged to the past Soviet Union have highest age-adjusted CHD mortality rates of all Asian countries, followed by other Middle East Asian and South Asian countries (**Fig. 1**).

Although developing countries have many barriers to improve STEMI care in general, there are several challenges particularly unique to India. These largely arise due to the distinctive structure of its healthcare system, which is one of the most privatized in the world[6]. Newer drugs combined with recognition of improved outcomes have prompted attempts to decrease the time from symptom onset to treatment delivery via Pre Hospital Thrombolysis (PHT). However, PHT is significantly superior to in-hospital thrombolysis (IHT). This is especially important in regions where PCI is not available. These newer, second-generation drugs for fibrinolytic therapy improve reperfusion rates and outcomes in STEMI patients.[7] Their bolus administration makes it possible to consider pre-hospital treatment in certain settings.

Reteplase is a novel plasminogen activator which was developed for the treatment of myocardial infarction. The molecule was designed by protein engineering to obtain a thrombolytic agent with a half-life that allows bolus injection and rapid and complete reperfusion of the occluded coronary artery[8]. Reteplase consists of the kringle 2 and the protease domains of t-PA and is not glycosylated at the consensus sequences (asparagines 184 and 448) due to its expression in *E. coli*[9]. Its half-life in patients is about 19 min compared to 3.3 min for alteplase structure of reteplase[10]. The *in-vivo* data showed a more rapid and complete reperfusion after bolus injection of reteplase when compared with other thrombolytic agents[11]. These features have been confirmed in clinical trials. There, reteplase achieved higher and faster reperfusion after two bolus injections of 10 units than 100mg infusion of alteplase[12]. The higher efficacy was not associated with more side-effects.

The overall efficacy and safety of MIRel™ (RLS brand of Reteplase) in patients with ST segment elevation Myocardial Infarction (STEMI) has been established in a controlled Phase III clinical trial and ongoing Post Marketing Surveillance (PMS) study. In this article, we have consolidated the data of two studies conducted in 284 patients.

Phase-III Clinical Trial

Methodology

It was a prospective, multi-centric, open-label study performed across fifteen centers in India. In the study, 83 patients were screened of whom 80 patients were enrolled in the study.

Patients with STEMI admitted to an intensive care unit in a hospital within 6 hours of onset of symptoms and

meeting all eligibility criteria, were enrolled in the study. Patients were followed at 30 minutes, 60 minutes, 90 minutes, 120 minutes, 6 hours, 8 hours, 12 hours, 16 hours, 24 hours, 48 hours, pre-discharge and at day 30 post treatment. ECG, hemogram, biochemistry, cardiac enzymes and echocardiography were performed at various intervals. Each patient received a total dose of 20 units of reteplase within 6 hours after the onset of AMI symptoms. The dose was given as two 10 unit intravenous injections each over two minutes, no more than 30 minutes apart. Patients at each site were enrolled only after receiving approval from the respective Ethics Committee. The study was conducted in compliance with the protocol, GCP and applicable regulatory requirements.

The primary objective of the study was to evaluate the all cause mortality rate at 30 days post-dosing in patients with STEMI following treatment with reteplase. The secondary objectives were to evaluate resolution of elevated ST segment at 90th minute post-dosing; evaluate rates of myocardial re-infarction(s) occurring within 30 days of post-dosing and evaluate rates of heart failure occurring within 30 days of post-dosing. The other secondary objectives were to evaluate changes in left ventricular ejection fraction (LVEF) occurring within 30 days post-dosing and evaluate events of ventricular tachyarrhythmias occurring within 30 days of post-dosing, the need for emergent or planned recanalization procedures (PTCA, stent and or CABG) occurring within 30 days of post-dosing. Safety assessment was based on treatment emergent adverse events, physical examinations, vital signs, ECGs, echocardiography and safety laboratory tests.

Patients

Male (70 patients) and female (10 patients) of 18 to 75 years of age ± SD presenting with AMI within six hours of occurrence of symptoms were included (i.e. ST elevation of ≥ 0.1 mV in two or more limb leads or ST elevation of ≥ 0.2 mV in two or more contiguous precordial leads). Patients were excluded if having following criteria: history of contra-indication to use of thrombolytics, patients with left bundle branch block (LBBB), internal active bleeding or known history of hemorrhagic diathesis, history of previous CVA, TIA of any kind, intracranial tumor, arteriovenous malformation, cerebral aneurysm, major surgery, parenchymal biopsy, ocular surgery and/or severe traumatism within six weeks prior to screening for study, the unexplained puncture in a non compressible vascular location in last 24 hours prior to screening, cardiogenic shock (systolic BP < 60 mm Hg), administration of any glycoprotein IIb/IIIa inhibitor in 24 hours prior to screening, patients on oral anticoagulant, suspected AMI secondary to occlusion of one lesion treated previously with a percutaneous coronary intervention, suspicion of aortic dissection, clinical pericarditis including pericarditis after present episode of acute myocardial infarction.

Statistical analysis

Statistically the study was considered successful with respect to 30 day mortality if the upper 95% confidence limit for 30 day all cause mortality rate was less than or equal to 13.0%. The proportion of patients achieving more than 50% lowering of ST segment levels at 90 minute post-dosing were presented with corresponding 95% confidence interval. Similarly, the proportions of patients with myocardial re-infarction, clinical symptoms of heart failure, changes in echocardiography, ventricular tachyarrhythmia and recanalization at 30 days were presented with 95% confidence intervals.

Results[13]

Efficacy analysis

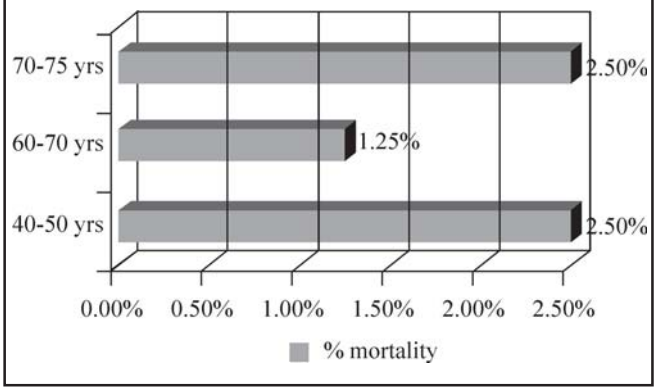
Primary efficacy

In the study, mortality was observed in five (6.25%) patients at 30 days post-dosing. The summary of mortality by cause is depicted below in **Table 1**. The summary of mortality by age is shown in **Graph 1**. All deaths happened at the hospital and none of them was related to study drug.

Table 1
Summary of mortality by cause

Cause of Death	Reteplase (N=80)
Acute extensive myocardial infarction with cardiac failure	1 (1.25%)
Acute left ventricular failure and acute renal failure	1 (1.25%)
Cardiac arrest	1 (1.25%)
Cardio respiratory arrest	1 (1.25%)
Ventricular tachycardia and fibrillation leading to cardiac arrest	1 (1.25%)

Graph 1
Summary of mortality by age



Secondary efficacy

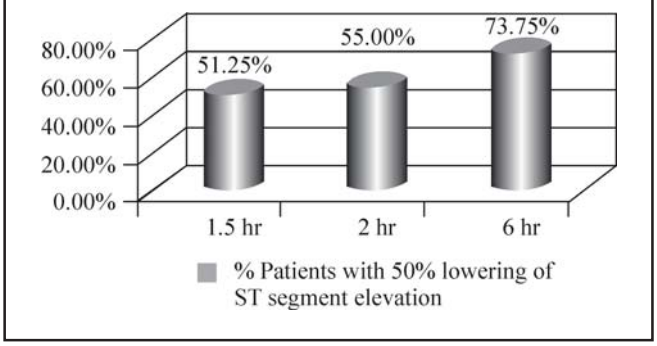
Resolution of elevated ST segment at 90th minute post-dosing

Out of 80 patients, 41 (51.25%) patients achieved 50% lowering of ST segment level at 90th minute, whose values lies within the range (0.40 to 0.62) of 95% confidence interval (**Table 2, Graph 2**).

Table 2
Summary of 50% lowering of ST segment elevation

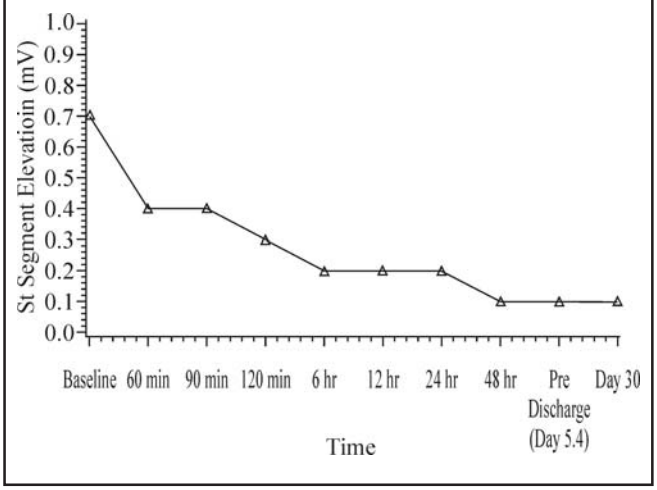
Variable	Reteplase (N=80)	
	n (%)	95 % CI
90 minutes	41 (51.25%)	(0.40, 0.62)
120 minutes	44 (55.00%)	(0.44, 0.66)
6 hours	59 (73.75%)	(0.64, 0.83)

Graph 2
% patients with 50% lowering of ST segment elevation



The following graph (**Graph 3**) represents mean ST segment elevation at baseline, 60 minutes, 90 minutes, 120 minutes, 6 hours 12 hours, 24 hours, 48 hours, pre-discharge and at the end of study. The mean ST segment elevation at baseline was 0.7 mV that was significantly resolved (p=0.0196) to 0.4 mV (42.80%) at 60 min. It continued to fall persistently until 48 hour and came at 0.1 mV.

Graph 3
Mean ST segment elevation



Myocardial re-infarction(s) occurring within 30 days post-dosing

There were total 3 (3.75%) patients, who experienced myocardial re-infarction within 30 days post-dosing.

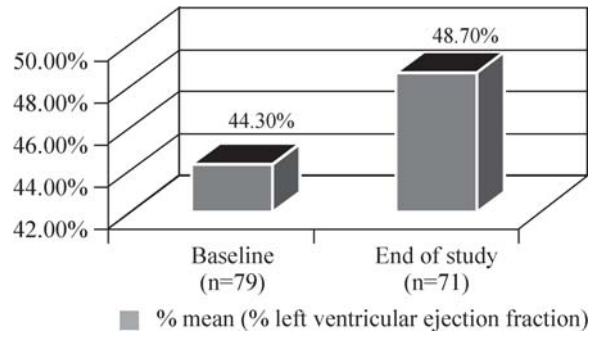
Heart failure occurring within 30 days post-dosing

There were 2 (2.50%) patients who developed symptoms of cardiac failure post-dosing during the study period.

Changes in left ventricular ejection fraction occurring within 30 days post-dosing

Ejection fraction was assessed by echocardiography. First Echo was done within 48 hours after admission and second, at the end of study visit (day 30). Mean left ventricular ejection fraction at baseline was 44.3%. There was significant improvement (p = 0.0002) in left ventricular ejection fraction at end of study i.e. 48.7%.

Graph 4
Summary of Cardiac function (LVEF)



Ventricular tachyarrhythmia occurring within 30 days post-dosing

There were total 4 (5.00%) patients who developed cardiac arrhythmia within 30 days post-dosing. There were no sinus bradycardia, supra-ventricular tachycardia, accelerated ideo-ventricular rhythm and ventricular pre-mature depolarization reported in the study.

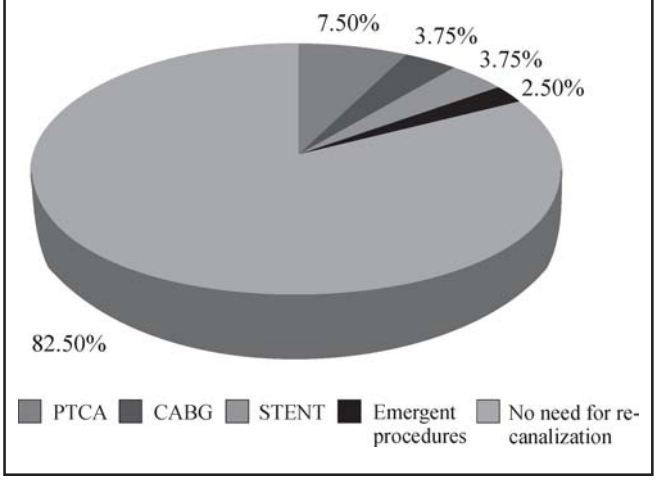
Table 3
Summary of Ventricular Tachyarrhythmia occurred within 30 days post-dosing

Variable	Reteplase (N=80) n (%)
Subjects with Cardiac Arrhythmia	4 (5.00%)
Number of Events	
Ventricular Tachycardia	3 (3.75%)
Ventricular Fibrillation	1 (1.25%)
Sinus Tachycardia	1(1.25%)
Sinus Bradycardia	0 (0.00%)
Supra-ventricular tachycardia	0 (0.00%)
Accelerated ideo-ventricular rhythm	0 (0.00%)
Ventricular pre-mature depolarization	0 (0.00%)

Need for emergent or planned recanalization procedures (PTCA, stent and or CABG) occurring within 30 days post-dosing

There were 14 (17.5%) patients, who underwent recanalization procedure. Most of the procedures, 12 (15.0%), were planned as per hospital policy. Only in 2 (2.50%) patients PTCA was done as an emergent procedure. Of planned procedures, there were 6 (7.50%) PTCA, 3 (3.75%) CABG and 3 (3.75%) STENT.

Graph 5
Summary of planned procedures



Safety analysis

The key concern of thrombolytic therapy is concomitant bleeding leading to stroke. In this study, no stroke was observed, while serious bleeding was observed in two patients only. One patient had gastrointestinal bleeding and other patient had gingival bleeding. There was no case of intracranial bleeding.

In this study, all adverse events were classified according to MedDRA version 10.1. Overall, there were 11 serious adverse events and amongst them mortality was observed in 5 (6.25%) patients. None of the deaths were related to study drug. There were no stroke events reported during study period.

The most common adverse events (occurrence ≥5% patients) were bradycardia, constipation, vomiting, chest pain, pain at study drug administration site, pyrexia, headache, cough and hypotension.

Most of adverse events were related to general disorders and administration site condition followed by cardiac disorders, vascular disorders and gastrointestinal disorders. General disorders and administration site conditions include pain, chills and pyrexia and pain at site of study drug injection (7.50%) that contributes 33.75% of adverse events. Cardiac

disorders contributed 31.25% of adverse events; most common of them were bradycardia, tachycardia and ventricular tachycardia. Gastrointestinal disorders (27.50%) mainly consisted of vomiting, constipation, nausea and gingival bleeding. Vascular disorders contributed 26.25% of adverse events that included hypotension (12.50%), thrombophlebitis (2.50%) and thrombosis (2.50%). Most frequent adverse event related to reteplase therapy was serious and non-serious bleeding that occurred in 7.50% patients in the study. About 2.50% patients required blood transfusion during study period, 7.50% patients experienced pain at study drug administration site.

Statistically significant fall was observed in platelet count ($p<0.0001$) post-dosing which was clinically non-significant. Rise in cardiac enzymes level was seen up to 8-hour post-dosing and then declined persistently which was consistent with myocardial infarction throughout the study. Coagulation profile of patients remained under control throughout the study. Hypotension was reported in 12.50% patients. Other important cardiac events reported were pericarditis (2.50%), bradycardia (8.75%), cyanosis (1.25%) and thrombosis (2.50%).

Post-marketing surveillance of Reteplase[14]

A Post Marketing Surveillance (PMS) following the marketing approval in India was undertaken to assess the safety profile of reteplase in patients with STEMI and/or recent left bundle branch block.

The study was initiated in India at specified sites in last quarter of year 2010. The safety data captured in the PMS study from October 2010 to June 2012 is provided herewith.

Reteplase was administered as two bolus injections of 10 units each. Each bolus is administered as a slow intravenous injection over 2 minutes. As per guidelines, no other medication was injected or infused in the same intravenous line. If reteplase is to be injected through an intravenous line containing heparin, a normal saline or 5% dextrose (D5W) solution was flushed through the line prior to and following the reteplase injection. The use of anticoagulants and antiplatelet drugs during and following administration of reteplase was advocated as per the updated guidelines from American Heart Association (AHA) and American College of Cardiology (ACC).

Total 204 patients' data was considered for the analysis in ongoing post-marketing study. The demography is given in the **Table 4** below. There were 166 (81.4%) male patients and 38 (18.6%) female patients enrolled. The mean age of patients was 58.5 years.

Table 4
Demographics and baseline characteristics

Variable	(N=204)
AGE	
N	204
Mean	58.5
SD	12.67
Median	59
Range	27, 85
SEX	
Male	166 (81.4%)
Female	38 (18.6%)

Results of post-marketing surveillance

There was one incidence of stroke reported (0.49%) in the PMS study. Only two (0.98%) patients had bleeding event i.e. one patient (0.49%) had retroperitoneal bleeding and one patient (0.49%) had intracranial bleeding. The different types of adverse events observed after reteplase administration is mentioned in table below (**Table 5**).

Table 5
Adverse events after reteplase administration (Pre-discharge)

Variable	Patients (N = 204)
Re-infarction	3 (1.47%)
Cardiac failure	9 (4.41%)
Bleeding events	2 (0.98%)
Cardiac arrhythmia	2 (0.98%)
Stroke	1 (0.49%)

Mortality observed in this study was in 8 (3.92%) patients which is lesser than Phase III study of reteplase in which mortality was observed in 5 (6.25%) patients (**Table 7**).

Patients who had undergone recanalization procedures during pre-discharge and post-discharge are mentioned in the following table (**Table 6**).

Table 6
Recanlization by type

Type	Reteplase (N = 204)
PTCA	27 (13.24%)
CABG	19 (9.31%)
STENT	12 (5.88%)

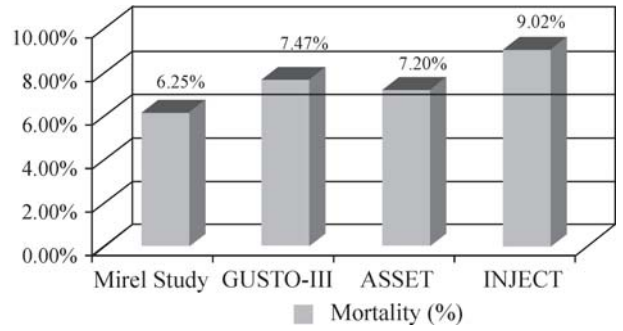
Discussion

Recombinant plasminogen activator (reteplase, r-PA) is a non-glycosylated deletion mutant of wild type tissue plasminogen activator (alteplase, t-PA) that is expressed in *Escherichia coli.* Unlike wild type plasminogen activator, reteplase lacks the kringle-1, finger, and growth factor domains of the molecule. These structural changes result in properties markedly different from those of t-PA, as has been demonstrated in both *in-vitro* and *in-vivo* studies[15,16]. Unlike alteplase, the nonglycosylated mutant of tissue plasminogen activator has less affinity for fibrin, a longer half-life, and greater thrombolytic potency. By virtue of a longer half-life (13-16 min), reteplase offers the potential advantage of administration by two bolus injections 30 min apart[17].

Reteplase has been evaluated for its efficacy and safety in Phase -III trial. In the study, mortality was observed in 5 (6.25%) patients at 30 days post-dosing. Study demonstrated that reteplase has significantly reduced mortality which is in line with earlier studies with reteplase (GUSTO-III – 7.47%, ASSET – 7.20%, INJECT – 9.02%).

41 (51.25%) patients achieved 50% lowering of ST segment level at 90th minute. Frequency of myocardial re-infarction was 3.75% with reteplase which is in line with other studies with reteplase (GUSTO-III – 4.20%, ASSET – 3.90%, INJECT – 5.00%).[18] Cardiac Failure was observed only in 2.50% patients. Mean left ventricular ejection fraction significantly (p = 0.0002) increased from baseline (44.3%) to end of study (48.79%). Overall incidence of cardiac

Graph 6
% Mortality in reteplase clinical trial



arrhythmia post-dosing was 5.00%. Ventricular tachycardia and ventricular fibrillation contributed 3.75% and 1.25% respectively. 2.50% patients required emergent recanalization procedure (PTCA) in the study.

Table 7
Efficacy Results

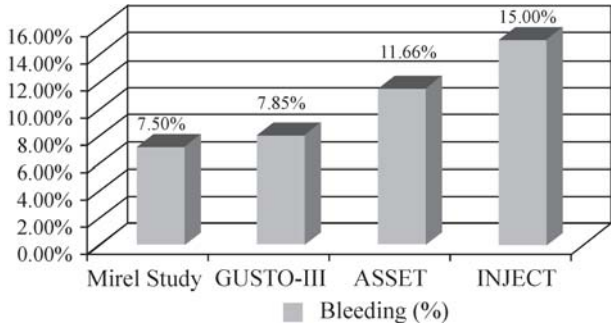
Variables	RETEPLASE (RLS Study on MIRel^{TM})
N	80
30 day mortality	6.25%
Re-Infarction	3.75%
Cardiac Failure	2.50%
Ventricular Tachyarrhythmia	3.75%
Ventricular Fibrillation	1.25%

The safety profile of reteplase is comparable with earlier reported reteplase studies. Bleeding events with reteplase therapy was 7.50% which is comparable to earlier reported studies (GUSTO-III – 7.85%, ASSET – 11.66%, INJECT – 15.00%) and only 2.50% patients required blood transfusion.

Stroke remained a complication reported in earlier studies (GUSTO-III – 1.64%, ASSET – 1.10%, INJECT – 1.23%) but no stroke event was reported in this study. Serious (2.5%) and non-serious (5%) bleeding was observed in 7.50% patients. There were 11 serious adverse events (SAEs) including 5 deaths, but none were related to study drug. Coagulation profile and vitals remained under control throughout the study and cardiac enzymes level

Graph 7

% Bleeding in reteplase clinical trials



showed persistent decline after 8-hour post-dosing which is consistent with thrombolytic therapy. Other cardiac complications: hypotension, pericarditis, bradycardia and thrombosis were less and in line with other reported studies.

Table 8
Safety Results

Variables	Reteplase (RLS Study on MIRel™)
N	80
Strokes	0.00%
Bleeding events	7.50%
Gastrointestinal	1.25%
Genitourinary	0.00%
Retroperitoneal	0.00%
Injection site	1.25%
Other	6.25%
Blood Transfusion	2.50%
Hypotension	12.50%
Cardiogenic shock	2.50%

In the current ongoing post-marketing surveillance of reteplase, different types of adverse events observed after reteplase administration are as follows: 3 (1.47%) patients had re-infarction, 9 (4.41%) patients had cardiac failure and 2 (0.98%) patients had cardiac arrhythmias. 2 (0.98%) patients had bleeding event i.e. one patient had retroperitoneal bleeding and 1 patient had intracranial bleeding. There were 8 deaths (3.92%) reported in the study which is lesser than Phase III study of reteplase in which 5 deaths (6.25%) were reported.

There was no new adverse event reported in the study.

Conclusion

Reteplase is a plasminogen activator, mimicking 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 t-PA that operates in the presence of fibrin. Reteplase can be administered as a bolus dose (non weight-based) rather than an infusion, which promotes rapid and safe administration. The ease of administration of this reteplase dosage regimen is conducive to prehospital initiation of thrombolytic treatment in patients with ST-segment elevation myocardial infarction (STEMI), which reduces the time to treatment, a critical factor in improving long-term survival. Reteplase significantly increased LVEF and had 50% lowering of ST-segment in more number of patients at 90 minutes post dosing.

Reteplase therapy in the two studies confers the safety and efficacy profile to be at par with the data from global clinical trials for reteplase. Reteplase provides a promising thrombolytic option to the medical fraternity for treating patients with STEMI.

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