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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

New Developments in Thrombolytic Therapy

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The use of accelerated tPA results in only 55–60% of patients experiencing early and complete infarction-related patency (TIMI 3). Modification of the tPA molecule has led to a number of new agents: rPA, uPA, and TNK-tPA. TNK has a prolonged half-life that allows it to be administered as a single intravenous bolus, and initial patency and safety profiles are encouraging. The GUSTO III study has compared tPA and rPA, and the other two agents will be studied in upcoming trials: In-TIME-2 (uPA), and ASSENT-II (TNK-tPA). This symposium reviewed the final results of GUSTO III and the phase-II studies that have paved the way for ASSENT-II. The role of mechanical revascularization (primary angioplasty/stent) alone or in combination with fibrinolytic and/or antithrombotic therapy was also discussed.

GUSTO III: Design and final results

rPA (reteplase), a deletion mutant of tPA (alteplase), has a longer half-life than tPA (13–16 minutes vs 3-6 minutes); which allows for a double-bolus administration rather than bolus and continuous infusion. Two randomized pilot studies (RAPID I and II)[1,2] suggested superior 90-minute infarction-related artery patency for rPA over tPA, and the double-blind study INJECT[3] showed rPA to be "at least equivalent" to standard streptokinase. It was hypothesized that 30-day mortality after acute myocardial infarction (MI) would be significantly reduced with rPA in comparison with accelerated tPA.

GUSTO III was an international, randomized comparison of double-bolus reteplase (10 U at 0 and 30 minutes) versus accelerated alteplase (maximum 100 mg over 90 minutes, as established in the landmark GUSTO I trial)[4] in patients presenting within six hours of onset of acute ST-segment elevation MI. Over 15,000 patients were enrolled at 807 hospitals in 15 countries with random assignments in a 2:1 ratio of rPA and tPA. Acetylsalicylic acid (ASA) was given to 97% of the patients. During the period of thrombolytic therapy, an intravenous heparin bolus of 5,000 U followed by an infusion adjusted to maintain an activated partial thromboplastin time (aPTT) at 50-70 seconds were given. No differences were found in the baseline characteristics of the two treatment groups. In comparison with the GUSTO I trial, the patients enrolled in GUSTO III tended to be older, included a higher percentage of females, had higher blood pressures at baseline, and had a greater prevalence of anterior MI and history of previous MI.

The total mortality at day 30 (the primary end-point of the study) was 7.47 in rPA- and 7.24 in tPA-treated patients (-0.23% difference, 95% confidence interval (CI): -1.12%, 0.66%). The 30-day rate of stroke was 1.64% in the rPA- and 1.79% in the tPA-treated groups. Additional end-points, including bleeding, in-hospital recurrent ischemia, reinfarction, and congestive heart failure, were similar among the two treatment groups. Taking into account the small but not statistically significant differences in mortality (favoring tPA) and stroke (favoring rPA), the net clinical benefit as defined

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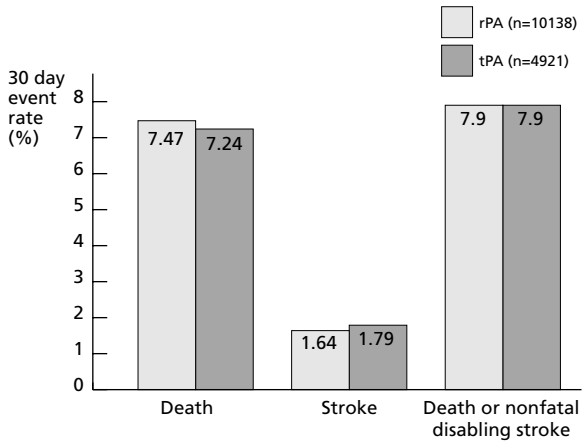
Figure 1: GUSTO III 30-day event rates



by 30-day mortality or non-fatal disabling strokes was 7.9% in both treatment groups (see Figure 1). Therefore, the expectation of a superior outcome from rPA treatment was not realized.

The GUSTO III Steering Committee concluded that, with 95% confidence, they could not exclude findings that the absolute mortality for accelerated tPA is 1.1% better than for rPA, or that mortality for rPA is 0.7% better than for accelerated tPA. Given that the superiority of accelerated tPA was established in GUSTO I (1% absolute, 14% relative reduction in 30-day mortality as compared to streptokinase, with maintenance of this benefit extended to one year follow-up), the results of GUSTO III cannot exclude superiority of tPA over rPA. Therefore, tPA continues to be the standard against which other thrombolytics must be compared.

It is interesting that, in subgroup analysis evaluating 30-day mortality stratified by time to treatment, there was a trend towards lower mortality among tPA- as compared to rPA-treated patients who received therapy more than four hours after symptom onset (7.9% vs 9.7%). This subgroup of patients receiving therapy beyond four hours represented 23% of all patients in the trial, and it raises the hypothesis that tPA might be superior to rPA beyond the four-hour treatment window. However, this is a post-hoc finding in one subgroup and is, therefore, far from conclusive.

TNK-tPA: Results of phase-II TIMI 10b and ASSENT-I

TNK-tPA is a combination mutant of tPA with a number of attractive features including a prolonged half-life (17-20 minutes), increased fibrin specificity, and plasminogen activator inhibitor-1 (PAI-1) resistance. In a phase-I dose-finding trial with TNK-tPA (TIMI 10a), TNK-tPA given as a bolus yielded coronary artery patency rates at 90 minutes similar to or slightly better than those observed with tPA in the GUSTO I trial.[5]

Recruitment into two larger phase-II trials has recently been completed: an angiographic efficacy study (TIMI 10b) comparing doses of 30 mg and 40 mg TNK-tPA with accelerated infusion of tPA; and a safety trial (ASSENT-I) evaluating the incidence of hemorrhagic stroke and major bleeding complications caused by these two doses of TNK-tPA. These two phase-II trials have enrolled a total of 4,211 patients and constitute the largest phase-II project ever undertaken in the field of thrombolysis. Indications are that the 40-mg dose of TNK-tPA will likely provide the greatest infarction-related artery patency without an increased risk of hemorrhage. It should be pointed out that the 50-mg dose administered during a high-dose heparin regimen was discontinued in these studies because of the finding of more frequent bleeding.

Compared to tPA, the 40-mg dose of TNK provided higher 60-minute TIMI-3 (complete) flow (58% vs 48%) and comparable 90-minute TIMI-3 flow (64% vs 63%).

ASSENT-I safety data showed an intracranial hemorrhage rate of 0.8%, a 30-day mortality rate of 5.6%, and an in-hospital reinfarction rate of 5.9% with the 40-mg dose of TNK. These event rates are certainly comparable (albeit in a much smaller number of patients) to those seen in GUSTO I with tPA, and they support doing a large-scale, phase-III comparative trial with accelerated tPA vs TNK-tPA.

ASSENT-II will be a double-blind, international trial in approximately 16,500 patients with acute ST-segment elevation MI presenting within six hours after symptom onset. The primary objective is to demonstrate equivalence in 30-day mortality between the two thrombolytic regimens. Recruitment is expected to start this month and will last approximately one year.

Pharmacologic and non-pharmacologic treatment of acute MI

There is overwhelming evidence that early, complete, and sustained reperfusion of the infarction-related artery plays a key role in the preservation of regional and global left ventricular function and, hence, favourable outcome. However, up to 40% of patients who receive aggressive therapy (accel-

erated tPA, intravenous heparin, and ASA) within six hours of onset of ST segment elevation MI do not experience complete (TIMI-3 flow) repatency. In addition to the new fibrinolytic agents (TNK-tPA, nPA), other pharmacologic and non-pharmacologic treatments are being explored.

Adjunctive medical therapy has focused mainly upon direct thrombin inhibitors (hirudin, hirulog) and antiplatelet therapies (glycoprotein IIb/IIIa inhibitors). Unfortunately, the direct thrombin inhibitors appear to have a very narrow therapeutic range. The GUSTO IIa,[6] TIMI 9a,[7] and HIT III[8] studies were all prematurely discontinued because of excess bleeding—particularly intracranial hemorrhage—due in part to hirudin. The GUSTO IIb[9] and TIMI 9b[12] studies proved reduced doses to be safe, but they failed to demonstrate reduction in death or myocardial infarction. Although there was an early, significant reduction in reinfarction with hirudin as compared to heparin therapy in patients with acute coronary syndromes in GUSTO IIb (either ST-segment-elevation MI and thrombolysis, or non-ST-segment-elevation MI or unstable angina), this benefit was not sustained. The early benefit in preventing (re)infarction was not seen in ST-segment elevation MI patients in TIMI 9b.

The experience with IIb/IIIa platelet inhibitors has been excellent in patients who have undergone percutaneous transluminal angiography (PTCA) and, more recently, in those with unstable angina or non-ST-segment-elevation MI. The upcoming GUSTO IV trial will evaluate a lower dose of tPA in combination with these powerful platelet inhibitors (abciximab).

Primary angioplasty has consistently produced very high reperfusion rates, and a meta-analysis of several small trials involving just over a thousand patients suggested that this approach yielded superior reduction in mortality and stroke rates as compared with the administration of thrombolytic therapy. The GUSTO IIb angioplasty sub-study[10] found a significant reduction in death and myocardial infarction at 30 days in those patients randomly assigned to angioplasty as compared to thrombolysis for ST-segment-elevation MI. However, the magnitude of this benefit was much less than suggested by the meta-analysis and, unfortunately, by six months this benefit was not sustained. Widespread use of primary angioplasty is obviously inhibited by time-to-treatment constraints and limited availability.

An early experience with angioplasty in those patients who had received thrombolytic therapy was described by O'Neil et al.[11] In this small, randomized trial, patients received placebo or streptokinase followed by angioplasty. There was a >90% success rate of angioplasty in restoring patency. However, 39% of the patients in the thrombolytic plus angioplasty group required red blood cell transfusions, as compared to only 8% in those who did not receive thrombolysis. Given the high bleeding and complication rates evident in this study and other limited experiences, interventionalists have been understandably reluctant to continue pursuing thrombolysis with early catheterization and angioplasty.

However, a post-hoc analysis was recently performed in 490 patients in the GUSTO-I trial who (for clinical reasons) underwent rescue angioplasty after thrombolytic therapy, revealing an 87-91% success rate in achieving infarction-related artery patency without an associated significant increase in bleeding complications. This has given rise to the concept of administering a larger initial bolus but lower overall dose of thrombolytic therapy and then evaluating the patient in the catheterization laboratory to assess infarct-related artery patency. If reasonable patency has been achieved with the initial bolus, as determined at the time of cardiac catheterization, the second bolus could be administered; however, patients with TIMI grade 0-2 flow (incomplete reperfusion) would instead undergo angioplasty.

This particular hypothesis has been evaluated in a randomized, placebo-controlled study: the Plasminogen activator Angioplasty Compatibility Trial (PACT). The study involved 606 patients randomly assigned to receive either placebo or 50 mg of tPA as a bolus. Patients then underwent catheterization to determine infarct-related artery patency, with further management as mentioned above. Repeat catheterization was undertaken at 5-7 days, and the results of this trial should be available by the spring of 1998.

While traditional thrombolytics and PTCA have been considered as an either-or choice, this new approach of rescue angioplasty and a modified, bolus fibrinolytic regimen could potentially avoid the frequent bleeding seen in lytic-treated patients having angioplasty, while improving early patency.

Conclusion

Great strides have been made in the treatment of patients with acute MI, as demonstrated by GUSTO I with only 10% mortality at one year. Further reduction in mortality will not be easy to achieve with thrombolytic modifi-

cation, although adjunctive treatment with antiplatelet and antithrombotic regimens and/or innovative use of PTCA will likely contribute further towards this goal. In the meantime, development of more fibrin-specific thrombolytics, like TNK-tPA, and bolus administration may improve safety and should enhance ease of treatment, which could potentially lead to earlier treatment of a larger number of patients. Based on promising angiographic and safety data with TNK seen in TIMI 10A and B and ASSENT-I, we eagerly await the results of the ASSENT II trial.

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