Safety and Efficacy of Tissue-Type Plasminogen Activator Produced by Recombinant DNA Technology

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Because of its enhanced activation of plasminogen in association with fibrin compared with free plasminogen, tissue-type plasminogen activator (t-PA) evoked excitement as a potentially useful pharmacologic activator of the fibrinolytic system. Initial studies in experimental animals and patients demonstrated that it induced coronary thrombolysis rapidly and without concomitant, marked fibrinogenolysis in contrast to streptokinase. Large scale clinical trials soon followed. Their results indicate that intravenous administration of t-PA produced by recombinant DNA technology (rt-PA) elicits coronary thrombolysis in two-thirds or more of treated patients with angiographically documented thrombotic occlusions generally without perturbing hemostatic mechanisms or inducing marked fibrinogenolysis. Bleeding is usually confined to vascular access sites and episodes of major bleeding are rare. Overall 6 week survival for treated patients with documented acute myocardial infarction may be as high as 95%.

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Fibrinolysis has been recognized for more than 200 years. Perhaps surprisingly, coronary thrombolysis has a relatively long history as well. The current intense interest in this mode of treatment of acute myocardial infarction reflects, in part, improved end points of efficacy (coronary angiograms that can be acquired safely in critically ill patients), increased appreciation of the seminal roles of thrombosis in the etiology of transmural myocardial infarction and reperfusion in the salvage of jeopardized tissue and the availability of activators of the fibrinolytic system with relative clot selectivity such as tissue-type plasminogen activator (t-PA) only recently synthesized successfully in pharmaceutical quantities by recombinant DNA technology (rt-PA).

Because of the relative clot selectivity of t-PA, a property reflecting its higher affinity for plasminogen in the fibrin domain than for circulating, free plasminogen, we evaluated human t-PA and subsequently rt-PA in experimental animals and patients with coronary thrombosis (1–5). Clot lysis was elicited promptly without marked fibrinogenopenia or induction of a systemic lytic state predisposing to bleeding. Subsequently, several large scale clinical trials were undertaken with rt-PA (6–10). Some of their results are the subject of this brief status report. Because this material addresses not only published results but also work in progress, some of the data are cited as personal communications provided by investigators before completion of manuscripts already being prepared, including material compiled by Drs. Chesebro, Grossbard, Mueller and Passamani.

The TIMI Trials

Phase I. The Thrombolysis in Myocardial Infarction (TIMI) trial conducted by the National Heart, Lung, and Blood Institute (NHLBI) has evolved through several phases to date. One (Phase I) documented an almost twofold greater incidence (62 compared with 31%) of angiographically confirmed coronary thrombolysis with rt-PA compared with streptokinase in a double-blind, prospective, random selection design (Fig. 1) (11). Significant but modest improvement of global and regional ventricular function has been evident in TIMI trial patients in whom reperfusion was induced by rt-PA within 4 hours of the onset of chest pain (12,13).

Mueller and her colleagues (14) delineated the incidence of bleeding in several phases of the TIMI trial to date (Fig. 2). The incidence of bleeding with streptokinase and rt-PA, the two activators used in Phase I, was similar. For rt-PA in all the phases of the TIMI trial analyzed by Mueller et al. bleeding was confined largely to vascular access sites (Fig. 3). Bleeding with rt-PA was generally but only loosely related to the magnitude of decreased fibrinogen and increased fibrinogen degradation products. Nevertheless, the associations support the view that laboratory criteria of a
systemic lytic state portend an increased risk of bleeding. Accordingly, the systemic lytic state seen invariably with even subtherapeutic doses of conventional activators is not likely to be entirely benign.

Compared with streptokinase, rt-PA lowers plasma fibrinogen markedly less judging from results in subsets of patients with extensive laboratory data analyzed in detail in both TIMI Phase I (data not shown) and the European Cooperative Trial (Fig. 4) (15). Major bleeding requiring transfusion occurs less frequently with rt-PA than with streptokinase, judging from results in the European Cooperative Trial (Fig. 5) (10,15).

Open label phases. Several open label phases of TIMI were undertaken in part to delineate optimal dose and duration of treatment with the originally produced rt-PA and with material available subsequently that comprised a larger fraction of so-called single chain (suspension culture, non-plasmin split) rt-PA. Despite some fluctuation of incidence, major bleeding occurred within a range of 7 to 25% with dose regimens that varied from 80 mg over 3 hours to 150 mg over 6 hours. Attempts to identify the upper bounds of safe dosage were motivated in part by the higher earlier recanalization rates (42 compared with 13% after 30 minutes) when 90 as opposed to 40 mg of rt-PA was given in the first hour. Furthermore, the higher doses of rt-PA used in TIMI open label phase E compared with those used in Phase I were associated with substantially higher rates of patency early (2 hours) and later (18 to 48 hours) after the onset of infusion (Fig. 6) (16). It was well recognized, however, based in part on data from several studies and with information obtained from computer-assisted analysis of pharmacodynamics (17), that consumption of alpha-antiplasmin indicative of risk occurs with doses and durations of infusion of rt-PA exceeding theoretically defined limits. Accordingly, the TIMI investigators and the TIMI policy board monitored each open label phase of the trial.

Figure 1. TIMI phase I—efficacy. Patency rates for patients treated with recombinant tissue-type plasminogen activator (rt-PA) (80 mg over 3 hours) or streptokinase (SK) (1.5 million U over 1 hour) in the double-blind, random patient selection, prospective study comprising Phase I of the TIMI trial. The number of subjects in the two groups was 113 and 119, respectively. rt-PA was more effective than streptokinase whether recanalization was defined by angiography 30 (hatched bars) or 90 (solid bars) minutes after the onset of administration of the active thrombolytic agent.

Figure 2. TIMI trial (total number = 850). Incidence of bleeding expressed as the percent of patients studied in the designated phases of the TIMI trial categorized as major, intracranial or total number of episodes whether minor or major. The percent of patients manifesting each type of episode in each of the phases specified in the trial is shown. Results in patients treated with streptokinase (SK) in Phase I are shown in the lowest section of the figure (n = 147). Those in patients treated with recombinant tissue-type plasminogen activator (rt-PA) in Phase I (n = 143) are represented by the bars immediately above. In open label phases A through E, all patients were treated with rt-PA but different doses were employed. The dose of rt-PA in Phase I was 80 mg over 3 hours (40, 20 and 20 mg/h, respectively). An identical dose of rt-PA prepared by a different production procedure in which a larger proportion of the product comprised material that had not been cleaved by plasmin (so-called single chain rt-PA) was used in open label phase A (n = 48). Because recanalization rates appear to be lower on a mg/mg basis with material produced by the newer procedures, the dose was increased to 100 mg over 3 hours (60, 20 and 20 mg/h, respectively) for open label phase B (n = 88). It was increased further to 150 mg over 6 hours (90, 20, 10, 10, 10 and 10 mg/h, respectively) for open label phase C. In each of these phases, infusions of rt-PA were initiated only after angiographic demonstration of coronary occlusion had been acquired. Subsequent open label phases of the TIMI trial employed administration of rt-PA without an initial angiogram and with the first angiogram performed 18 to 48 hours (phase D, n = 42) or either 2 hours or 18 to 48 hours (phase E) after the onset of administration of rt-PA in a total dose of 150 mg over 6 hours (n = 317). Because phase E was performed in an open label fashion with vigorous surveillance of possible bleeding complications in light of what was recognized to be a very high dose of rt-PA, 53 of the 317 patients were treated in this phase after an adjustment had been made to a lower dose (100 mg over 6 hours; 60, 20, 5, 5, 5 and 5 mg/h, respectively) on October 21, 1986.
Figure 3. Compilation of bleeding episodes in 344 patients studied in TIMI Phases I, A, B and C. Most episodes of bleeding were associated with vascular access sites. Additional information pertinent to bleeding in specific phases of the TIMI trial and to specific dose regimens particularly with respect to intracranial bleeding is summarized in Ref. 18. As noted in that communication, a 1.6% incidence rate of intracranial bleeding (5 of 311 patients) occurred among patients treated with 150 mg. In view of this experience, the dose was reduced to 100 mg for patients treated subsequently in the TIMI trial. In the remaining 53 patients studied in TIMI open label phase E who were treated with the 100 mg dose, no intracranial bleeding occurred. Cath = catheterization site; GI = gastrointestinal tract site.

Figure 4. Fibrinogenolysis (after Collen et al. [15]). Changes in plasma fibrinogen after 1 hour expressed as a percent of control values with data obtained with either a precipitation (sulfite) (solid bars) or kinetic (striped bars) assay after 60 minutes of treatment with recombinant tissue-type plasminogen activator (rt-PA), streptokinase (SK) or neither agent (control) in 131 patients with acute myocardial infarction. The number of patients in each group is indicated in parentheses. Patients evaluated were among those studied in the European Cooperative Trial (10,15).

Figure 5. Hemorrhagic events within 48 hours after infusion of recombinant tissue-type plasminogen activator (rt-PA) (0.75 mg/kg over 90 minutes) or streptokinase (SK) (1.5 million U over 60 minutes) in patients studied by Verstraete et al. (10) in the European Cooperative Trial. Both the incidence of major bleeding and the overall incidence of bleeding were less among patients treated with rt-PA.

Figure 6. Patency rates. Comparison of infarct-related coronary artery patency evident angiographically 90 minutes after the onset of infusion of recombinant tissue-type plasminogen activator (rt-PA) in 429 patients with initially occluded coronary arteries documented by preinterventional angiography in Phase I (40, 20 and 20 mg of rt-PA infused over 3 hours) and 2 hours or 18 to 48 hours after the onset of infusion of rt-PA to patients without preinterventional angiography but with criteria of evolving transmural myocardial infarction fulfilling the TIMI entry criteria in open label phase E of the TIMI trial (90 mg of rt-PA given in the first hour). Results in both groups (Phase I and phase E) are compared with the incidence of patency evident in preinterventional angiograms available for the Phase I patients only. The higher doses of rt-PA used in open label phase E compared with those used in Phase I were associated with a somewhat greater rate of early patency.
of recurrent myocardial infarction (MI) or extension of infarction during both intervals. Episodes of intracranial bleeding (IC) were included in the tabulation as deaths. Even with the classification of such bleeding episodes as "mortality," survival throughout the hospital course and throughout a 6 week interval of follow-up after infusion of rt-PA was unusually high (94%) for patients with documented acute transmural myocardial infarction.

arrests) with the 100 mg dose of rt-PA over 6 hours and the virtual absence of intracranial bleeding in patients treated with the 100 mg dose to date.

Among 400 patients treated with 120 to 170 mg of rt-PA over intervals comparable with those employed in TIMI open label phase E and studied in clinical trials monitored by the Genentech Corporation, the incidence of intracranial bleeding within 48 hours of infusion of rt-PA was <0.5%. Among 998 patients treated with equipotent regimens of rt-PA produced by diverse production modes over the past several years it was only 0.3% (19). Among analogous trials conducted in Europe involving 781 patients it was 0.26% (E. Grossbard, personal communication).

Therapeutic failures. When intracranial bleeding and death are considered together as criteria of failure of therapy with rt-PA, only 5% of 317 patients given 150 mg of rt-PA were adjudged to have had therapeutic failure throughout their entire hospitalization in open label phase E of the TIMI trial. Only 6% were adjudged to have had therapeutic failure throughout a 6 week interval of follow-up (Fig. 7) (E. Passamani, personal communication). Patency occurred in 87% of 220 patients, judging from results of angiography 18 to 48 hours after treatment. When the dose regimen in open label phase E was modified to 100 mg of rt-PA over 6 hours, efficacy remained apparently constant. The incidence of intracranial bleeding at this dose has been low (none among the 53 patients treated with 100 mg in open label phase E).

Side effects. Administration of rt-PA does not generally induce an immune response. Positive results for detection of antibodies to rt-PA by radioimmunoprecipitation assay have been seen in only three samples from >700 patients tested worldwide (E. Grossbard, personal communication). In no case were the antibodies neutralizing. In each case, subsequent samples evaluated 3 weeks to 10 months after treatment were negative.

Mild, febrile reactions or urticaria have been encountered in <10% of TIMI patients treated. Deleterious hemodynamic effects attributable to rt-PA have not been encountered. Although as many as 40% of patients treated with rt-PA have experienced nausea and vomiting, it is difficult to determine the extent to which these and other nonspecific phenomena are attributable to rt-PA as opposed to narcotics, other medications or infarction in progress.

Conclusions

End point results to date from the two largest prospective, randomized patient assignment, double-blind trials with rt-PA (the TIMI trial and the European Cooperative Trial) are concordant and compatible with those of smaller studies with native t-PA and rt-PA as well as with those of studies of rt-PA combined with angioplasty (20-22). In concert, the data indicate that: 1) Intravenous rt-PA elicits recanalization promptly in >70% of patients—a success rate comparable with that documented with maximal doses of intracoronary streptokinase; 2) rt-PA depletes circulating fibrinogen and elevates circulating fibrinogen degradation products much less than does streptokinase, as reflected by results of prospective, randomized, clinical trials (15,23); 3) bleeding associated with administration of rt-PA under research protocol conditions generally involving large doses of heparin concomitantly is confined generally to vascular access sites and is readily manageable; and 4) early treatment with rt-PA is associated with remarkably low hospital and 6 week mortality among patients with documented acute transmural myocardial infarction.

Figure 7. Mortality and morbidity throughout the hospital course and throughout a 6 week interval of follow-up among 317 patients treated with recombinant tissue-type plasminogen activator (rt-PA) in open label phase E of the TIMI trial as well as the incidence of recurrent myocardial infarction (MI) or extension of infarction during both intervals. Episodes of intracranial bleeding (IC) were included in the tabulation as deaths. Even with the classification of such bleeding episodes as "mortality," survival throughout the hospital course and throughout a 6 week interval of follow-up after infusion of rt-PA was unusually high (94%) for patients with documented acute transmural myocardial infarction.

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References


