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Reviews

New Plasminogen Activators: A Clinical Review

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Summary: Rapid restoration of patency of the infarct-related artery is the key to preserving myocardium and improving survival. This understanding has led to the application of genetic engineering to develop new plasminogen activators with specific clinical features. These novel activators may provide faster and more complete reperfusion in a greater number of patients, and do so with less risk of bleeding and intracranial hemorrhage. This article reviews the pharmacologic profiles and clinical performance of several novel plasminogen activators engineered from the human tissue plasminogen activator molecule or developed from animal and bacterial proteins.

Key words: thrombolysis, plasminogen activators, acute myocardial infarction, TNK-tissue plasminogen activator

Introduction

Thrombolytic agents given in a timely fashion to patients with acute myocardial infarction (MI) have been conclusively shown to reduce mortality.[1] Angiographic investigations have further documented that restored infarct-related artery patency, via the mechanism of preserving left ventricular (LV) ischemic (but not yet necrotic) myocardium, is the underlying mechanism effecting this benefit. The Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries-I (GUSTO-I) angiographic substudy (and others) established these relationships: patients treated with recombinant tissue plasminogen activator (rt-PA) in an accelerated ("front-loaded") regimen achieved the desired early patency nearly twice as often as patients given the less effective streptokinase, which then translated to a 14% relative decrease in 30-day deaths (and an absolute reduction in mortality from 7.3 to 6.3%).[2] The ratio, then, of increased rate of full patency (TIMI grade 3 flow) to lives saved calculates to approximately 20 more open arteries required to save one additional life.[3] Commonly utilized plasminogen activator treatments have historically left over a third of infarct arteries still occluded.

While patency of the infarct artery is the principal goal, rapidity of reperfusion is equally important. Opening vessels early in the infarct course is considerably more salutary than achieving patency later.[4] Logically, therefore, substantial efforts have been underway to design new thrombolytic strategies capable of producing even higher initial patency rates than those accomplished with the current standard of reference, the 90-min rt-PA infusion. Simultaneously, investigators are seeking ways of reducing the time from MI onset to reperfusion, both by earlier treatment strategies and by promoting faster clot lysis once treatment is initiated.

Four complementary approaches are being followed:[5–8] (1) improving time to treatment, through efforts including bolus delivery of agents and prehospital administration of drugs; (2) use of more potent adjunctive agents [e.g., direct antithrombins and glycoprotein (GP) IIb/IIIa receptor inhibitors] than aspirin and heparin, the current standards; (3) combination strategies such as a lytic agent followed by rescue angioplasty when TIMI flow is less than grade 3; and (4) development of new plasminogen activators that will, through specific molecular features, produce higher rates of TIMI grade 3 flow and faster action. These approaches have produced several novel plasminogen activators engineered from the human t-PA molecule or developed from animal and bacterial proteins. Table I describes the characteristics of these agents. Phase III clinical trials now underway with these agents are expected to conclude early in 1999.

Thus, the familiar thrombolytic landscape will change. For this reason, it is appropriate to update the pharmacologic profiles and clinical performance of agents introduced or under active investigation since streptokinase, anisoylated plasminogen activator complex (APSAC, anistreplase) and rt-PA became available, and since the status of the newer agents was summarized by the author in 1997.[9]

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TABLE I Key characteristics of newer thrombolytic agents compared with t-PA

Characteristic	Alteplase (t-PA or rt-PA)	Reteplase (rPA)	Saruplase	TNK-t-PA	Lanoteplase (nPA)	Staphylokinase	Vampire bat PA
Immunogenicity	No	No	No	No	?	Yes	Yes
Plasminogen activation	Direct	Direct	Direct	Direct	Direct	Indirect	Indirect
Fibrin specificity	++	+	+	+++	+	+++	+++
Plasma half-life	4–6 min	18 min	9 min	20 min	37 min	6 min	2.8 h
Dose	15 mg bolus plus 90 min infusion up to 85 mg	10+10-MU double bolus 30 min apart	20 mg bolus + 60 mg infusion over 1 h	±0.5 mg/kg single bolus	120 KU/kg single bolus	15 mg + 15 mg double bolus over 30 min	0.5mg/kg single bolus
PAI-1 resistance	No	?	?	Yes	?	?	?
Genetic alteration to native t-PA	No Recombinant version	Yes Finger, EGF, and kringle-1 regions deleted	No Prodrug of single-chain urokinase	Yes 2 single amino acid substitutions in kringle-1 and substitution of 4 amino acids in catalytic domain	Yes Finger, EGF regions deleted and glycosylation sites in kringle-1 domain modified	No Modified strain *S.aureus*	No Native bat-derived protein

Abbreviations: t-PA = tissue plasminogen activator, rt-PA = recombinant t-PA, EGF = epidermal growth factor.

Reteplase (rPA)

Reteplase (rPA) is a deletion mutant of t-PA in which the finger, epidermal growth factor (EGF), and kringle-1 regions of the wild-type t-PA molecule have been deleted. These mutations produce a molecule with a prolonged half-life (18 min, almost 4-fold greater than alteplase). The longer half-life of rPA permits administration as a double bolus given 30 min apart.[10] Initial enthusiasm about this agent was based on what appeared to be superior patency at 90 min in the early RAPID I and RAPID II trials, which enrolled 606 and 324 patients, respectively.[11,12] In retrospect, the small number of subjects in the rt-PA arms of these trials (145 in RAPID I, 155 in RAPID II) suggests that the difference observed was not actually the result of a higher patency rate with rPA, but rather reflects an unusually low success rate with rt-PA (Table II), which was probably due to chance.

In the Recombinant Plasminogen Activator Angiographic Phase II International Dose-Finding Study (RAPID I), the 90-min rate of TIMI grade 3 flow was 62.7% with rPA (n = 142), compared with 49% for rt-PA (n = 145); in RAPID II, the difference was 59.9% with rPA (n = 157) versus 45.2% with rt-PA (n = 146).[11,12] In the GUSTO-III trial, which enrolled more than 15,000 patients from 807 hospitals in 20 countries, the 30-day mortality rate was 7.47% among recipients of reteplase and 7.24% for alteplase; a small difference, but outside the boundaries that would permit concluding that rPA is equivalent to rt-PA. Thus, reteplase provided no additional survival benefit over alteplase.[13]

That the apparently superior patency of rPA observed in the RAPID trials did not result in a mortality advantage in the much larger GUSTO III trial might be explained by several factors. First, as the GUSTO III investigators pointed out, it is possible that the patency advantage for rPA observed in the smaller RAPID trials was due only to the play of chance.[13] Second, it is believed that achieving patency very quickly is the most important factor in preventing death.[2] The rate of very early patency (within 30 min) in RAPID II was higher with rt-PA than with rPA (39 vs. 27.3%, but not statistically

TABLE II Variability in 90-min TIMI 3 patency reported for t-PA

t-PA trials (Ref.)	Date	N	90-min TIMI 3 patency (percent of patients)
TAPS (54)	1992	199	66–78
GUSTO-I (1, 2)	1993	292	48–60
TIMI 4 (34)	1994	127	52–69
TIMI 10B (32)	1997	296	63
TIMI 14 (52)	1998	35	60
Combined mean TIMI 3 patency with t-PA			61
RAPID I (11)	1995	145	49
RAPID II (12)	1996	146	45.2

Abbreviations: TIMI = Thrombolysis in Myocardial Infarction trial, TAPS = The Alteplase APSAC Patency Study, RAPID = Recombinent Plasminogen Activator International Dose-finding study.

significant),[12] which may offset the later patency advantage of rPA.

Finally, there is some evidence suggesting that rPA is associated with a greater incidence of reocclusion than rt-PA. This notion is supported by the fact that rPA—as a function of the deletion mutation used to create the drug—is less fibrin specific than rt-PA.[12, 14] In addition, there is evidence that rPA activates platelets to a markedly greater degree than does rt-PA.[15] Concerns about the danger of reocclusion have led to a common belief that if clinicians choose to use rPA, they should consider using it in combination with a potent antiplatelet agent (a GP-IIb/IIIa antagonist), an approach utilized in the ongoing GUSTO IV trial.

Recombinant, Single-Chain Urokinase-Type Plasminogen Activator (r-scu-PA, Saruplase)

Saruplase, also known as recombinant single-chain urokinase-type plasminogen activator (r-scu-PA) or prourokinase, is a prodrug produced from a naturally occurring, physiologic protease. This well-studied agent is a single-chain polypeptide consisting of 411 amino acids. In vivo, it is partially converted by plasmin into an active, two-chain, low-molecular weight form of urokinase with 276 amino acids.[16, 17] In addition, the unconverted fraction of saruplase activates plasminogen directly.[14] The half-life of saruplase in patients is 7 to 8 min.[17]

Saruplase causes systemic plasminemia in patients, as evidenced by decreases in alpha-2 antiplasmin and fibrinogen and an increase in fibrinogen degradation products.[18] Systemic fibrinolytic activity is less than that of streptokinase, but greater than that of alteplase.[19, 20]

The Practical Applicability of Saruplase Study (PASS),[21] carried out in 1,698 patients with acute MI, confirmed the safety and efficacy of a saruplase regimen consisting of a 20 mg bolus followed by a 60 mg infusion over 60 min. All saruplase regimens include—indeed they require—concomitant infusion of heparin and are enhanced by a preliminary bolus of heparin.[22]

Subsequent trials have been performed with the PASS regimen. In the Study in Europe with Saruplase and Alteplase in Myocardial Infarction (SESAM),[23] saruplase and the now superseded 3-h infusion of rt-PA produced similar 90-min TIMI 2/3 flow rates (79.9 and 81.4%, respectively). Reocclusion was infrequent with both drugs (1.2 percent with saruplase, 2.4% with rt-PA), and complication rates were not significantly different between the treatment groups.

In the 401-patient Prourokinase in Myocardial Infarction trial (PRIMI),[24] 60-min coronary patency was significantly higher with saruplase than with streptokinase, although there were no significant differences between the two agents when examined at the time periods of 90 min and 24 to 36 h. The rate of intracranial hemorrhage (ICH) was considerably higher with saruplase.

The recent Comparison of Saruplase and Streptokinase (COMPASS) trial, designed to demonstrate equivalence of saruplase and streptokinase in 3,089 patients, found a trend toward a lower incidence of all-cause mortality at 30 days with saruplase compared with streptokinase (5.7 vs. 6.7%, respectively).[25] Overall rates of stroke and reinfarction were likewise similar in the two groups. However, it was found that the rate of ICH was considerably higher with saruplase (0.9%) than with streptokinase (0.3%).

In further research, saruplase is being modified and coupled with t-PA in chimeric variants of plasminogen activator. One example is a chimera consisting of the two kringle domains of t-PA and the serine protease domain of saruplase. In animal models, this modification has produced greater thrombolytic potency than either alteplase or saruplase alone, mainly because of a prolonged half-life. The new substance has also been given successfully in a double-bolus regimen to a small number of patients.[26] In still other experiments, saruplase has been chemically cross-linked with antifibrin and antiplatelet antibodies or their Fab fragments, with the aim of concentrating the thrombolytic at the site of the thrombus. The combination has produced a 29-fold enhancement of thrombolytic potency in vivo (rabbit jugular vein thrombus model) compared with saruplase alone.[27]

TNK-Tissue Plasminogen Activator

TNK-t-PA is a t-PA mutant that was specifically bioengineered to preserve the full fibrinolytic activity of wild-type t-PA while significantly improving upon the native molecule in a number of ways. Bioengineered features include reduced drug clearance: TNK-t-PA is cleared more than four times more slowly from plasma than native t-PA, thus permitting TNK-t-PA to be administered as a single bolus, with the attendant advantages of convenience and longer duration of effect. As part of its molecular modification, TNK-t-PA carries fibrin specificity 14-fold greater than that of wild-type t-PA. The highest level of fibrin specificity may be desirable in a thrombolytic agent because it permits targeting of the infarct-related clot while minimizing systemic plasminogen activation.[28]

Another feature of TNK-t-PA is its 80-fold greater resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1). Plasminogen activator inhibitor-1 is the primary regulator of the fibrinolytic system and a major inhibitor of exogenous t-PA. The lytic action of plasminogen activators affects primarily the fibrin-rich ("red") portion of coronary thrombi, exposing the large pool of clot-bound thrombin. As thrombin is a potent activator of platelets, this partial lysis stimulates further aggregation of platelets, thereby increasing the concentration of PAI-1 near the site of lytic activity.[29] Therefore, enhanced resistance to PAI-1 appears to be a desirable feature for a lytic agent. There is also evidence that TNK-t-PA is intrinsically less thrombogenic than other plasminogen activators. DeMarco *et al.* found no increase in thrombin-antithrombin complex (TAT) after administration of this agent, in contrast to a four-fold increase following streptokinase and a doubling after rt-PA.[30]

Early clinical evidence indicates that single-bolus TNK-t-PA is as effective as the parent t-PA in producing lysis of the infarct-related artery.

The main efficacy evidence comes from the Thrombolysis in Myocardial Infarction (TIMI) 10 trials. In TIMI 10A,[31] a single-bolus, dose-ranging, angiographic trial, the effects of eight different doses (5, 7.5, 10, 15, 20, 30, 40, and 50 mg) were followed in 113 patients with acute MI. TIMI grade 3 flow at 90 min ranged from 57 to 64% in patients receiving doses of 30 to 50 mg, as shown in Figure 1. These rates are similar to or slightly better than those observed with accelerated rt-PA[2] and reteplase.[11,12] Efficacy was achieved with a low incidence of major bleeding (6.2%) which was seen most often at the vascular access site. TNK-t-PA had minimal effects on systemic coagulation, as assessed by average decreases in fibrinogen (3%) and, more specifically, in plasminogen (13%) and α-2-antiplasmin (25–30%).

The TIMI 10B trial was an angiographically controlled study of 886 patients randomized to 30 or 50 mg boluses of TNK-t-PA or the accelerated regimen of rt-PA.[32] Shortly after the trial began, the 50 mg bolus of TNK-t-PA was replaced by a 40 mg dose, because the former was associated with a heightened risk of ICH. The ICH risk was, in part, attributed to overdosage of heparin and resulted in heparin-dose reduction for patients weighing < 67 kg.[33] The 40 mg dose of TNK-t-PA produced TIMI grade 3 flow in 57% of patients, well within the range achieved with the accelerated rt-PA regimen as shown in Table II.[32] The rate of serious bleeding events was similar for both agents.

The TIMI 10A and 10B trials are noteworthy for their original use of the TIMI Frame Count to evaluate patency. This method measures reperfusion more objectively by counting the number of angiographic frames required for contrast material to reach standard distal landmarks in the coronary arterial bed.[34] In TIMI 10A, 62 to 68% of patients receiving TNK-t-PA had TIMI frame counts of < 40, and 45% of these patients had frame counts of ≤ 27.[31] In TIMI 10B, average frame count in patent vessels was 28.7 in the 40 mg TNK-t-PA group and 32.6 in patients receiving accelerated rt-PA ($p = 0.05$).[35,36]

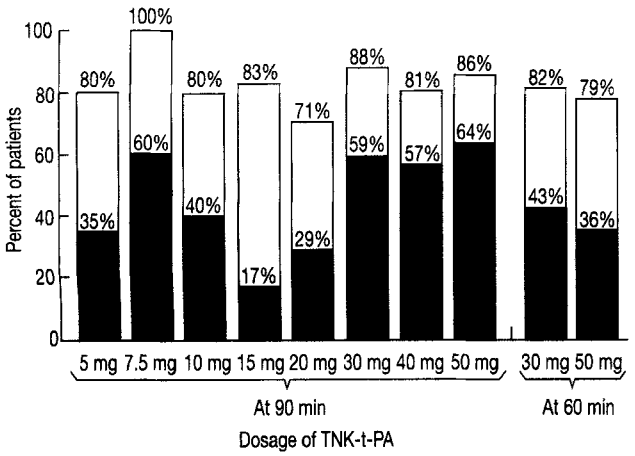

FIG. 1 TIMI flow grade 2 and 3 at 90 min across 8 doses of TNK-t-PA and at 60 min for 30 and 50 mg doses: TIMI 10A. □ = TIMI 2, ■ = TIMI 3.

The Assessment of the Safety of a New Thrombolytic I (ASSENT I) trial was conducted in parallel with TIMI 10B to assess the safety of TNK-t-PA. The trial's 3,325 patients with acute MI received a single bolus of TNK-t-PA in a dosage of 30, 40, or 50 mg (the latter was subsequently discontinued). The 40 mg dose had an ICH rate of 0.76%, comparable to what has been observed with rt-PA.[8] These data were the basis for selection of a weight-based dose of TNK-t-PA, using a simple four-step dosage scheme, in further clinical testing of TNK-t-PA. The phase III ASSENT II trial of 16,500 patients is in progress as an equivalence study of TNK-t-PA and rt-PA, with a 30 day-mortality end point.

A final issue relative to TNK-t-PA is speed: it produces 60-min TIMI grade 3 flow rates comparable with what is achieved only at 90 min by other agents. It is also speedily delivered since it can be given as a single bolus, as can the next agent to be discussed, lanoteplase (nPA).

Lanoteplase (nPA)

Lanoteplase (nPA) is a deletion and "point" mutant of wild-type t-PA, in which the finger and EGF domains of the t-PA molecule have been removed and the glycosylation points in kringle 1 have been modified.[10,37] The altered molecule, produced in Chinese hamster ovary cells, has a half-life of approximately 37 min, improved lytic activity (relative to native t-PA) in animal models, and reduced fibrin affinity. Its clearance and half-life make nPA suitable for single-bolus delivery.[38]

The phase II, 602-patient dose-ranging trial known as Intravenous nPA for Treatment of Infarcting Myocardium Early (InTIME)[39] evaluated single boluses of 15, 20, 60, and 120 U/kg nPA against accelerated rt-PA. A clear dose–response relationship was observed with nPA. At 90 min, the highest dose of nPA appeared to be more effective than rt-PA: TIMI grade 3 flow was 57% with nPA and 46% with rt-PA ($p = 0.11$). There were no differences in the 30-day composite end point of death, heart failure, major bleeding, or nonfatal reinfarction, although event rates were somewhat higher in the rt-PA group. Plasma clearance of nPA was slower than that of rt-PA, and plasma half-life was longer.[40]

Similar to the early experience with rPA, the appreciably higher patency rate reported with nPA may be more reflective of an unusually low TIMI 3 flow rate in the smallish number of control (rt-PA) patients than of a high patency rate with this new agent. Confidence in the success rate with lytic drugs requires a sample of several hundred patients due to multiple patient factors that influence patency—factors other than the fibrinolytic's potency.[41] Table II shows the variability of 90-min TIMI 3 flow rates with accelerated rt-PA. Combining multiple studies of this regimen, one might reasonably conclude that about 60% of infarct-related arteries reach TIMI 3 flow after administration of accelerated rt-PA. This outcome is different from the 40, 45.2, and 46% TIMI 3 flow rates reported for the small rt-PA arms in the RAPID I (rPA),[11] RAPID II (rPA),[12] and InTIME (nPA)[39] trials.

The follow-up phase III study, InTIME-II, has been designed as an equivalence trial against rt-PA with the primary end point of mortality. This trial has a target sample size of 15,000.

Staphylokinase

Recombinant staphylokinase is a plasminogen activator of bacterial origin (strains of *S. aureus*) consisting of a single polypeptide chain of 136 amino acids. Like streptokinase, it does not convert plasminogen to plasmin directly but forms a 1:1 stoichiometric complex with plasminogen. The staphylokinase-plasminogen complex is inactive until it is converted to an active staphylokinase-plasmin complex by plasminogen activators.[7,37,42]

Staphylokinase was first studied as a thrombolytic agent in canine models in the 1960s, with unremarkable results and unacceptable side effects due to contaminants in purification. After cloning and expression of the gene in the 1980s, recombinant staphylokinase was produced nearly free of contaminants and its thrombolytic properties were reevaluated in humans.[42] One of the attractive features of staphylokinase is its high fibrin specificity. In the absence of fibrin, staphylokinase is quickly neutralized by alpha-2 antiplasmin (whereas streptokinase is not). However, in the presence of fibrin, staphylokinase is highly resistant to alpha-2 antiplasmin neutralization at the clot surface.[26,42] The result is localized fibrin degradation and limited systemic plasminogen activation. Moreover, once it has digested a fibrin clot, the staphylokinase-plasmin complex is released and inhibited by alpha-2 antiplasmin so that further plasminogen activation is interrupted.[42]

In the Recombinant Staphylokinase (STAR) study,[43] 100 patients with acute MI were randomized to treatment with a 10-mg infusion of staphylokinase or accelerated rt-PA. Poor TIMI-3 flow rates—50% at 90 min—prompted a decision to double the dose of staphylokinase. With the 20-mg dose, TIMI grade 3 flow rose to 74%, compared with the lower but not significantly different 58% seen with rt-PA. However, staphylokinase was significantly more fibrinogen sparing. Levels of circulating fibrinogen, plasminogen, and alpha-2 antiplasmin were unchanged in patients receiving staphylokinase but decreased markedly in the rt-PA group. No allergic reactions or ICHs were observed, and rates of bleeding did not differ significantly with the drugs. It is difficult to draw conclusions from mortality figures in a 100-patient trial. Thus, the significance of five in-hospital deaths in the rt-PA group versus none in the staphylokinase group is uncertain.

Like streptokinase, staphylokinase is a protein of nonhuman origin and therefore triggers an immune response in patients. Antibodies develop in the majority of patients within 2 weeks after initial administration and persist for at least 7 months.[37,44] It is not clear, however, whether these antibodies can induce allergic reactions. No reactions were reported in the first 300 patients treated,[45] a finding that may be due to the low molecular weight of the staphylokinase molecule (compared with streptokinase).[16]

An accurate assessment of allergic reactions would require about 10,000 treated patients.[44] Current evidence suggests that use of staphylokinase, in the current molecular derivative known as sakSTAR, will need to be restricted to a single administration. However, because antibodies elicited by staphylokinase do not crossreact with streptokinase,[46] consecutive administration of these drugs may be possible. It is also reported that compounds resulting from site-directed mutagenesis of specific amino acids of the STAR molecule have induced significantly less antibody formation in animals and patients without sacrificing thrombolytic activity.[42,47] Further testing of these compounds will be necessary to determine whether it is possible to avoid immune reaction to staphylokinase.

An ongoing trial being conducted primarily in Canada will compare staphylokinase and accelerated rt-PA in 480 patients. This will be followed by a large mortality trial that will compare staphylokinase with either streptokinase or rt-PA.[48]

There are several unresolved questions with staphylokinase. Among these is the question of whether bolus dosing will prove successful (the substance's half-life is only 6 min).[44] Some studies of bolus delivery have been encouraging.[46]

Vampire Bat Salivary Plasminogen Activator (bat-PA)

Saliva of the vampire bat (*desmodus rotundus*) contains a family of four plasminogen activators called desmodus salivary plasminogen activators (DSPAs). Of these, DSPA alpha-1, or bat-PA, is the longest protein (477 amino acids) and, structurally, the most homologous to human t-PA. It consists of a finger domain, an EGF domain, and a single kringle structure, but lacks the second kringle domain and the plasmin cleavage site necessary for conversion to a two-chain form of plasminogen activator.[26,44] This latter trait makes bat-PA the only plasminogen activator known to exist exclusively as a single-chain molecule with full catalytic activity.[26] Bat-PA is produced by recombinant technology in mammalian cells.[44]

Bat-PA is highly fibrin specific and has demonstrated faster and more sustained reperfusion than human t-PA in animal models.[49,50] Reperfusion is accomplished with no degradation of systemic fibrinogen and only small decreases in plasminogen and alpha-2 antiplasmin levels.[49] While bleeding time with bat-PA has been comparable with that with human t-PA, bat-PA has caused a much greater number of protracted bleeding episodes than t-PA.[51] In the only clinical trial of bat-PA reported to date, the drug's half-life was 2.8 h, a feature that would allow for single-bolus administration in clinical use.

Like staphylokinase and other nonhuman proteins, bat-PA has the potential for provoking an immune response. Single-bolus administration of 10 mg has induced antibody formation in animals, especially after repeat administration, with antibodies detectable for at least 32 to 49 weeks. Allergic reactions were not observed.[44] Until trials now in progress with bat-PA are completed and reported, it will not be known whether the substance can offer any advantages beyond those of the native t-PA molecule.

Other Approaches

Since plasminogen activators attack the fibrin but not the platelet component of coronary thrombus, the concept of combining activators with platelet aggregation inhibitors more potent than aspirin is quite appealing. This approach could be additionally attractive if more profound platelet inhibition would allow successful coronary thrombolysis with lower doses of the plasminogen activators and, hence, potentially lower treatment-related cerebral hemorrhage incidence. Combinations of rt-PA, rPA, and streptokinase with GP IIb/IIIa inhibitors have initially suggested such desirable outcomes. In the TIMI 14 trial, a low, 35 mg dose of rt-PA plus the GP IIb/IIIa inhibitor abciximab produced TIMI 3 flow at 90 min in 71% of patients.[52] In the same study, 1.5 million units of streptokinase produced TIMI 2/3 flow in more than 80% of patients. However, this combination was associated with a prohibitively high incidence of bleeding.

A discussion of the virtues of primary angioplasty as an alternative reperfusion modality is beyond the scope of this discussion. However, an interesting approach under investigation is the use of thrombolytic regimens given to patients in advance of intended cardiac catheter laboratory interventions in an effort to lessen the delay encountered by many patients selected for an interventional approach. In the Plasminogen Activator-Angioplasty Compatibility Trial (PACT), 606 patients with acute MI were enrolled in a double-blind, randomized trial in which alteplase was given immediately before coronary angiography and, if indicated by lack of TIMI 3 flow, underwent immediate percutaneous transluminal coronary angioplasty (PTCA) of the infarct-related artery. Prior thrombolytic therapy with alteplase did not compromise the technical and clinical efficacy of PCTA, did not lead to an increase in bleeding complications, and had a beneficial clinical effect on early reperfusion.[53]

Conclusions

Thrombolytic therapy has had a remarkable impact on the treatment of acute MI, having reduced 30-day mortality from 20 to 25% at 30 days to the range of 7 to 8% in the context of clinical trials; however, its potential remains to be fully realized. Refinements and innovations in treatment regimens may provide faster and more complete reperfusion in a greater number of patients, and do so with fewer complications. Several new approaches that will compete for clinical acceptance have been reviewed herein. The results of new clinical trials with these agents are awaited with great interest.

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