Combination Pharmacotherapy for Achievement and Maintenance of Vascular Patency

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Abstract—Acute ischemic stroke results from an abrupt interruption of focal cerebral blood flow. In the majority of cases, this interruption is caused by an acute thromboembolism. Arising from the clinical trials in acute myocardial infarction, combination pharmacotherapy is gaining significant interest as a potential method to improve current thrombolytic treatment in acute ischemic stroke. This article reviews the scientific rationale and available evidence for the potential options to improve current pharmacologic therapy for achieving and maintaining vascular patency in acute ischemic stroke. (Stroke. 2009;40[suppl 1]:S99-S102.)

Key Words: reperfusion • pharmacotherapy • vascular patency

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 glorolecular experience in acute therapies for myocardial infarction includes a number of combinations of fibrinolytics at varying doses and other agents proposed to speed recanalization, improve the degree of recanalization, and prevent reocclusion. This body of literature is now being used as the basis for clinical research attempts to improve outcomes in ischemic stroke.

The formation of a thrombus is a highly dynamic process and is dependent on both the activation of platelets, leading to platelet aggregation, and the activation of the coagulation cascade, leading to fibrin formation. As such, pharmacologic regimens meant to open occluded arteries may be optimized if they include agents that work in opposition to these forces. In addition, early reocclusion occurs in 34% of tissue-type plasminogen activator (tPA)–treated patients with any initial recanalization, accounting for two thirds of the number of cases of deterioration after improvement.1 This offers further evidence that additional agents should be considered to not only augment initial fibrinolysis but also help maintain patency after lysis.

Likely candidates to augment thrombolysis would be those that combat the dynamic formation of clots, such as antiplatelet medications or anticoagulants. This article will review recent exploration into pharmacologic combination therapy for achievement and maintenance of vascular patency in acute ischemic stroke.

Anticoagulants

Logical methods to augment thrombolysis can be identified by evaluating the competing processes that occur during fibrinolytic therapy, such as the activity of thrombin during fibrinolysis. In the early phase of fibrinolysis, the activity of an exogenous fibrinolytic agent is counterbalanced by the continuous, endogenous generation of thrombin. As fibrinolysis progresses, the partially lysed thrombus exposes internal fresh thrombin which can lead to activation of platelets and generation of fibrin, which compete with thrombolysis and may lead to reocclusion. Early effective inhibition of thrombin will shift the balance away from thrombogenesis and toward thrombolysis, thereby increasing the recanalization rate and shortening the time delay to reperfusion. In addition, effective thrombin inhibition will also prevent reocclusion after successful thrombolysis by inhibiting platelets.

One promising direct-acting thrombin inhibitor, argatroban, selectively inhibits both free and clot-associated thrombin. An important advantage of argatroban over other thrombin inhibitors is its short half-life, which allows rapid offset of action in case of bleeding. In animal stroke models, argatroban safely augmented the benefit of recombinant tPA (rt-PA) by improving flow in the microcirculation, increasing the speed and completeness of recanalization, and preventing reocclusion.2–6 In 1 large human trial of acute myocardial infarction treatment wherein argatroban and rt-PA were combined, argatroban appeared to enhance reperfusion with rt-PA in patients with acute myocardial infarction better than heparin in a dose-dependent fashion. In addition, the incidences of major bleeding and adverse clinical outcomes were lower in patients who received argatroban.7

One important pilot trial has been published on the combination of rt-PA plus argatroban in acute ischemic stroke patients. The ARGatroban Anticoagulation in Patients with Acute Ischemic Stroke (ARGIS-1) Study showed that argatroban given within 12 hours of ischemic stroke provides
safe anticoagulation without an increase in intracerebral hemorrhage (ICH). However, in this small sample, no clinical benefit was observed.

Subsequently, the first phase of the ARGatroban tPA Stroke Study (ARTSS) has been published. This is an ongoing prospective, open-label, dose-escalation, safety, and activity study of argatroban and rt-PA in patients with ischemic stroke. The primary outcome was the incidence of ICH, and the secondary outcome was complete recanalization at 2 hours. After standard-dose intravenous rt-PA administration, a 100-µg/kg bolus of argatroban followed by infusion of 1 µg/kg per minute for 48 hours was given and adjusted to a target partial thromboplastin time of 1.75 times that of the control group.

In this first phase, 15 patients (including 10 men) were enrolled, with a mean ± SD age of 61 ± 13 years. All patients had middle cerebral artery occlusions. Baseline median National Institutes of Health Stroke Scale (NIHSS) score was 14 (range, 4 to 25). The mean ± SD time from symptom onset to argatroban bolus administration was 172 ± 53 minutes. Symptomatic ICH occurred in 2 patients, including 1 with parenchymal hemorrhage type 2. Asymptomatic bleeding occurred in 1 patient and there was 1 death. Recanalization was complete in 6 patients and partial in another 4, and reocclusion occurred in 3 within 2 hours of rt-PA bolus administration. The investigators concluded that the safety of low-dose argatroban combined with intravenous rt-PA may be within acceptable limits and its efficacy for producing fast and complete recanalization is promising, but a larger cohort of patients is required to confirm these preliminary observations. This shows the theoretical promise of the addition of thrombin inhibition to fibrinolysis. There are human data for acute myocardial infarction as well as pilot safety data in acute ischemic stroke, but additional data are necessary to determine the potential for a phase III clinical trial.

Another study of the use of anticoagulants and tPA in the setting of acute ischemic stroke sought preliminary data on immediate post–rt-PA therapy to prevent reocclusion. Recalling that early reocclusion occurs in 34% of rt-PA–treated patients with any initial recanalization, these investigators studied low-molecular-weight heparin (LMWH) given immediately after rt-PA. The patients received either standard anticoagulation starting 24 hours after intravenous rt-PA or anticoagulation with 2850 IU nadroparin, given every 12 hours immediately after rt-PA. In this pilot safety trial of 60 patients, 25 received standard anticoagulation 24 hours after rt-PA and 35 received LMWH started immediately. Symptomatic ICH occurred in 1 patient (4%) in the delayed anticoagulation group and in 3 patients (8.6%) in the early anticoagulation group (odds ratio [OR] = 1.8; 95% CI = 0.2 to 12.8). At 3 months, 9 patients in the standard delayed anticoagulation group (36%) and 16 patients in the immediate anticoagulation group (45.7%) achieved a modified Rankin Scale score of 0 or 1 (OR = 1.2; 95% CI = 0.5 to 3.2). According to the authors, the study suggested that treatment with LMWH could be associated with higher odds of ICH, although it may not necessarily lead to a worse outcome. The authors believe that the results justify larger clinical trials.

Thus, there is the potential to augment the recanalization capability of rt-PA with the addition of a direct-acting thrombin inhibitor as well as the potential to prevent an all too common complication (reocclusion) with the early administration of LMWH. Although these are preliminary trials, they offer hope for future study.

**Antiplatelet Agents**

Research in acute coronary syndromes has demonstrated that platelet glycoprotein (GP) IIb/IIIa antagonists, whether alone, in combination with reduced doses of thrombolytic agents, or as complementary therapy for acute mechanical interventions, merit consideration as a class of agents for use in ischemic stroke. As described earlier, the formation of a thrombus is dependent on both the activation of platelets, leading to platelet aggregation, and the activation of the coagulation cascade, leading to fibrin formation. Platelet activation is initiated by a number of mechanisms, such as exposure of the platelet to the thrombogenic stimulus of vessel injury or atherosclerotic plaque rupture. Once activated, platelets undergo a number of changes, including a change in the conformation of the GP IIb/IIIa surface membrane receptors. These receptors are unique to platelets and megakaryocytes, with each platelet having ≈80 000 copies of the receptor on its surface. Regardless of the agonist that initiated platelet activation, this conformational change in the GP IIb/IIIa receptor leads to the aggregation of platelets via binding of the platelets at the GP IIb/IIIa receptors, as well as the binding of platelets with multivalent molecules such as fibrinogen and von Willebrand factor. Fibrinogen and von Willebrand factor can bind >1 platelet and thus provide cross-linking for thrombus formation. Whereas both fibrinogen and von Willebrand factor are available for cross-linking in thrombus formation, fibrinogen exists in vastly greater concentrations in the serum as well as in granules released by activated platelets and is therefore the dominant molecule for platelet cross-linking. Repetition of the process of platelet-to-platelet binding and platelet-to-fibrin binding leads to platelet thrombus formation; however, this description oversimplifies the complex process of thrombus formation. The focus on the final common pathway—the GP IIb/IIIa receptor change and subsequent platelet-to-platelet binding and platelet-to-fibrinogen binding—does point out the significance of this receptor as a potential target for therapies for acute ischemic processes due to thrombosis. Finally, the fact that GP IIb/IIIa binding is reversible and competitive offers additional promise for pharmacologic intervention.

With the understanding that acute ischemic stroke is usually due to a thromboembolism and accepting that the aggregation of platelets and the associated cross-linking with fibrin are central to thrombus formation, the potential therapeutic use of an antagonist to the activated GP IIb/IIIa receptors can then be envisioned. If platelet aggregation and fibrinogen cross-linking can be adequately disrupted by a GP IIb/IIIa antagonist, then acute vascular occlusion by a platelet-rich thromboembolus may be relieved by disaggregation of the platelets and subsequent dissolution of the offending thromboembolus. Furthermore, the combination of platelet disaggregation and fibrinolysis may be a powerful
therapeutic combination. In fact, the potential utility in the setting of acute clot is considerable. Current use of fibrinolytics only has significant disadvantages. Whereas the fibrin component of a thromboembolus in acute ischemic stroke may be sensitive to lysis by plasminogen activators, the aggregated platelets resist dissociation.\textsuperscript{12,13} In addition, in the setting of coronary fibrinolysis, platelets accumulate at the clot surface, thereby slowing clot dissolution.\textsuperscript{14} Moreover, rt-PA has been shown to stimulate platelet aggregation and may potentially promote microthrombosis extension.\textsuperscript{15} The potential to augment thrombolyis and/or prevent vascular occlusion via platelet aggregation inhibition has led to pilot trials of rt-PA plus GP IIb/IIIa inhibitors.

Previously published experience with this combination therapy for acute ischemic stroke is limited but shows promising results. Morris et al\textsuperscript{16} described 5 patients treated with 0.45 mg/kg rt-PA and full-dose abciximab with 12 hours of infusion. Three of the 5 patients had a >6-point decline on the NIHSS score at hospital discharge compared with pretreatment. The series had 1 asymptomatic parenchyma hematoma in the area of infarction. The authors concluded that a larger placebo-controlled trial was needed.

Straub et al\textsuperscript{17} reported on 21 patients treated with a combined protocol who had acute middle cerebral artery occlusions as demonstrated by magnetic resonance angiography. Of these, 2 patients were lost to follow-up and 19 were described. The patients were treated with intravenous rt-PA (a single 20-mg bolus in 15 cases or a 10-mg bolus followed by a 40 mg intravenous infusion over 1 hour in 4 cases). They also received the GP IIb/IIIa antagonist tirofiban at a dose of 0.4\textmu g/kg per minute for 30 minutes followed by an infusion of 0.1 \textmu g/kg per minute for at least 48 hours. This represents the GP IIb/IIIa regimen studied in the PRISM PLUS cardiac trial and can be expected to produce \textgtr80% platelet aggregation inhibition (full cardiac dosing).\textsuperscript{18} No symptomatic ICH or systemic hemorrhages were reported. Recanalization was judged by 24-hour magnetic resonance angiography to be TIMI grade 2 or 3 in 13 of 19 patients (68\%) and TIMI grade 3 in 10 patients (53\%). The authors concluded that prospective, randomized, placebo-controlled multicenter trials are needed.

Additional published series have described varied regimens of intravenous GP IIb/IIIa antagonists in combination with intra-arterial rt-PA, with stent placement, or as rescues after failed standard intravenous rt-PA. The common theme to these articles, however, is that platelet aggregation inhibition in combination with fibrinolysis is promising and merits further exploration.\textsuperscript{19–22}

One published series retrospectively reviewed 37 consecutive patients with ischemic stroke who were treated with systemic application of low-dose rt-PA and body weight–adjusted tirofiban (a nonpeptide GP IIb/IIIa receptor antagonist). Patients in the rt-PA plus tirofiban group were compared with a group of patients treated with a dose 0.9 mg/kg rt-PA at a different center (rt-PA group n=119). The patients treated with rt-PA plus tirofiban and the rt-PA group reached a Rankin Scale score of 0 to 2 in 63\% and 55\%, respectively. Death rates were similar among the 2 treatment groups, including 1 fatal hemorrhage in the rt-PA plus tirofiban group (8\%) and 4 fatal hemorrhages in the rt-PA group (5\%). The authors concluded that systemic combined thrombolysis with rt-PA plus tirofiban “seems to be a feasible treatment in acute stroke.”\textsuperscript{23}

The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA (CLEAR) Stroke Trial, which assessed the safety of treating acute ischemic stroke patients within 3 hours of symptom onset with combination therapy, was recently completed.\textsuperscript{24} The CLEAR trial was a National Institutes of Health/National Institute of Neurological Disorders and Stroke–funded multicenter, double-blind, randomized, dose-escalation, and safety study. Patients were randomized 3:1 to either low-dose rt-PA (tier 1=0.3 mg/kg, tier 2=0.45 mg/kg) plus eptifibatide (75 \textmu g/kg bolus followed by 0.75 \textmu g/kg per minute infusion for 2 hours) or standard-dose rt-PA (0.9 mg/kg). The primary safety end point was the incidence of symptomatic ICH within 36 hours. Secondary analyses were performed regarding clinical efficacy.

The trial enrolled 94 patients (40 in tier 1 and 54 in tier 2). The combination group of the 2 dose tiers (N=69) had a median age of 71 and a median baseline NIHSS score of 14, and the standard rt-PA group (n=25) had a median age of 61 years and a median baseline NIHSS score of 10 (P=0.01 for NIHSS score). Fifty-two (75\%) of the combination group and 24 (96\%) of the control group had a baseline modified Rankin Scale score of 0 (P=0.04). There was 1 (1.4\%; 95\% CI=0\% to 4.3\%) symptomatic ICH in the combination group and 2 (8.0\%; 95\% CI=0\% to 19.2\%) in the rt-PA–only arm (P=0.17). During randomization in tier 2, the independent Data Safety Monitoring Board review demonstrated that the safety profile of the combination therapy at the tier 2 doses was such that further enrollment was statistically unlikely to indicate inadequate safety for the combination group, the ultimate outcome of the study. Thus, the study was halted. The investigators concluded that the safety of the combination of reduced-dose rt-PA plus eptifibatide justified further dose-ranging trials in acute ischemic stroke.

On the basis of the notable safety of the combination in CLEAR but the lack of a sign of efficacy compared with standard-dose rt-PA, the CLEAR-Enhanced Regimen (CLEARER) Stroke Trial will be performed. This multicenter, double-blind, randomized safety study is designed to provide data concerning the risks and benefits of a combined regimen of intravenous low-dose rt-PA (0.6 mg/kg) and eptifibatide versus standard-dose (0.9 mg/kg) rt-PA. The trial is proposed to enroll 126 patients in a 5 to 1 ratio. This will result in a total of 105 patients being treated with the combined regimen and 21 patients being treated with standard-dose intravenous rt-PA alone.

The primary specific aim of this study is to obtain reliable estimates of the safety of an enhanced dosing regimen of eptifibatide in combination with 0.6 mg/kg rt-PA in acute stroke patients in whom treatment is begun within 3 hours of symptom onset. Secondary aims are to determine whether the estimated efficacy of combination therapy in acute ischemic stroke warrants proceeding to a large phase III randomized trial and, if so, to obtain data that will allow determination of the sample size needed for that trial.
Conclusions

Fibrinolysis for acute ischemic stroke has changed the management of this disease process. Attempts to refine the process are in clinical trials. Combinations of a fibrinolytic plus either an anticoagulant or antiplatelet agent offer considerable potential to improve achievement of arterial patency and maintenance of that patency once achieved. Although multiple exploratory trials have been encouraging, definitive efficacy trials remain relatively far on the horizon.

Disclosures

None.

References

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