Emerging Therapies

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Hemostatic Treatment in the Early Stage of Intracerebral Hemorrhage
The Recombinant Factor VIIa Experience

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The treatment of intracerebral hemorrhage (ICH) has been a largely neglected item. In contrast to literally dozens of clinical trials of treatment of ischemic stroke, only a handful have addressed treatment of ICH with either medical (steroids,1 osmotic diuretics2) or surgical3 interventions. The medical intervention trials, primarily aimed at reducing brain edema surrounding the ICH, have shown lack of benefit of treatment with dexamethasone1 or glycerol solutions.2 Although some pilot data suggested a potential benefit of early surgical drainage of the hematoma,4,5 the recent publication of neutral results in the large, prospective, and randomized international Surgical Trial in Intracerebral Hemorrhage (STICH) study6 has been a disappointment. Mendelow and colleagues went for 8 years of enrollment and follow up of over 500 subjects in each treatment group, one managed “conservatively,” the other subjected to surgical drainage of the hematoma within a maximum of 4 days from symptom onset. The final results showed no benefit of one mode of treatment over the other, because a favorable outcome occurred as frequently in the “conservative” (24%) as in the surgical (26%) group when they were evaluated at 6 months. Although a prespecified subgroup analysis suggested a possible advantage of surgical treatment for superficially located (<1 cm from the cortical surface) lobar hematomas, the overall trial results showed that only one fourth of patients with ICH can be expected to have a good clinical outcome, which cannot be improved on by surgical treatment. In the wake of the neutral STICH trial results, it is refreshing to see some hope for the treatment of this devastating stroke subtype with the publication of the results of the phase IIB trial of recombinant activated factor VIIa (rFVIIa) in ICH.7 Mayer et al assessed the value of different doses of rFVIIa (NovoSeven; Novo Nordisk) on decreasing the early enlargement of the hematoma (primary outcome) and compared this effect with clinical secondary outcomes measured at 90 days. The results were encouraging, because each of the 3 doses of rFVIIa (40, 80, 160 μg/kg) given within 4 hours of symptom onset to close to 100 patients per group were followed by a reduction in hematoma growth in comparison with placebo; the mean relative increase in ICH volume was 11% for the highest rFVIIa dose (160 μg/kg), which was significantly lower than the 29% observed in the placebo group, whereas the intermediate doses (40 and 80 μg/kg) showed a trend toward lower volume increases as well (16% and 14%, respectively). The 3 rFVIIa groups combined had a significant reduction of absolute ICH growth (4.2 mL) in comparison with placebo (8.7 mL; P=0.01). These beneficial effects on early hematoma growth were correlated with survival and with favorable clinical outcomes (defined as 0 to 1 in the modified Rankin Scale, 7 to 8 in the Extended Glasgow Outcome Scale, 95 to 100 in the Barthel Index, and 0 to 1 in the National Institutes of Health Stroke Scale score) at 90 days. Both outcomes favored rFVIIa-treated subjects, who had an 18% mortality for the 3 groups combined in comparison with 29% for the placebo group (P=0.02). Similarly, death and severe disability combined occurred in 69% of placebo patients and in 53% of those treated with rFVIIa, an absolute risk reduction of 16% (P=0.004). This clinical effect translated into a number needed to treat of approximately 6 to prevent one unfavorable outcome.

The enthusiasm generated by these preliminary results has to be tempered, however, by some of the findings reported. The most important one relates to the observed increased frequency of thromboembolic complications in the subjects treated with rFVIIa (7%, in comparison with 2% for the placebo group). Although this difference was not significant (P=0.12), it raises a concern about the range of patients likely to derive a net benefit from this therapy. The thromboembolic complications in the rFVIIa-treated group were predominantly arterial (16, for a total of 21 events), whereas the 2 events in the placebo group were venous, thus amounting to a rate of 5% of arterial events (7 myocardial and 9 cerebral infarcts) in the rFVIIa group versus none in the placebo group (P=0.01). Because one half of the 16 arterial events in the rFVIIa group occurred in the highest-dose (160 μg/kg) group (a dose twice as high as that recommended for the treatment of bleeding in patients with hemophilia8), it is possible that the use of lower doses may result in a reduction of risk for this complication. This approach is being tested in the ongoing phase III FAST (rFVIIa in Acute...
Hemorrhagic Stroke Treatment) international trial, in which doses of 20 and 80 μg/kg of rFVIIa are compared with placebo. The results of this study will be crucial for the assessment of efficacy of the intermediate doses of rFVIIa with a hopefully reduced frequency of arterial thromboembolic complications. The demonstration of a positive net benefit of rFVIIa in the ongoing phase III trial will be required to justify consideration of extending the use of this agent to situations of high risk of ICH enlargement such as in warfarin-related ICH. Although rFVIIa at a mean dose of 62.1 μg/kg (range, 15 to 90 μg/kg) was safe (without thromboembolic complications) in a small study of 7 patients with warfarin-related ICH, patients with this type of ICH are likely to be particularly prone to the thromboembolic complications of rFVIIa. This risk will be added to that posed by the discontinuation of warfarin in the setting of conditions requiring this agent for cerebral and systemic embolism prevention such as chronic atrial fibrillation or mechanical heart valves.

There are other caveats to consider. One is that the study of Mayer et al. showed that the benefit of rFVIIa was evident after the treatment was initiated within 3 hours of symptom onset. The 269 patients treated within that time period had a 13% increase of ICH volume in comparison with 34% for the placebo group (P = 0.004), whereas 115 patients treated more than 3 hours after onset had no difference in hematoma growth (16%) in comparison with the placebo group (14%). This observation suggests that the time of active hematoma growth (and thus available for intervention) may be limited to this short window, and only patients treated early will benefit from this therapy. The larger ongoing FAST trial should further clarify this issue, because the same 4-hour window of the phase IIIB trial has been maintained in the protocol.

Another issue of potential importance is the fact that in the analysis of clinical outcomes in the trial, there was no adjustment for blood pressure, a factor known to affect the outcome of ICH, and there was no protocol-mandated uniform management of hypertension throughout the trial. The blood pressure was elevated at baseline in all 4 treatment groups to a similar degree (mean of 178/97 mm Hg, with little variation among groups), and the decline that was observed at 24 hours (mean of 154/85 mm Hg) and at 72 hours (mean of 150/80 mm Hg) showed no apparent differences among the treatment groups.

This would suggest that differences in blood pressure control did not account for part of the benefit from rFVIIa in the trial. Attention to these issues in future trials will likely identify possible interactions of rFVIIa with blood pressure as determinants of the magnitude of the benefit for patients with ICH.

Finally, there is a theoretical concern about an increase in perihematoma edema with treatment with rFVIIa, because this agent acts by enhancing thrombin generation on the surface of activated platelets, and thrombin has been implicated in the pathogenesis of edema formation around an acute experimental ICH. This phenomenon, which has been correlated with a high plasma concentration of the proinflammatory molecule TNF-α (tumor necrosis factor-α) in humans, could potentially contribute to the local mass effect of the acute ICH and thus lead to early neurologic deterioration. However, such an effect was not observed in the earlier dose-escalation phase II trial. Similarly, in the larger phase IIIB trials, the mean volume of the combination of ICH, intraventricular hemorrhage, and perihematoma edema at 72 hours remained essentially stable (and significantly smaller than in the placebo group) across the 3 doses of rFVIIa.

In conclusion, there is a justified enthusiasm about the potential of rFVIIa as an effective new therapeutic approach to ICH, after the promising results of the phase IIIB, proof-of-concept study reported by Mayer et al. The results of the ongoing phase III FAST trial should further clarify a number of important issues about this promising agent, including its most effective and safe dose, its potential treatment interaction with blood pressure control, and the future feasibility of testing rFVIIa in patients with other types of ICH, in particular those with warfarin- and thrombolysis-related hemorrhages.

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