Is It Time to Definitely Abandon Neuroprotection in Acute Ischemic Stroke?

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See related article, pages 1751–1758.

Since the ischemic penumbra was discovered and since a therapeutic window for acute ischemic stroke has been postulated, stroke experts are looking for safe and effective drugs to treat as many acute ischemic stroke patients as possible.

Maturation of ischemic damage is a complex process, triggered by hypoperfusion at critical levels and spontaneously evolving toward cell death. It is a self-perpetuating process in which some critical steps (such as ion pumps failure and iNOS production) maintain and enhance the process.1

Reperfusion may reverse the ischemic cascade but, at the same time, induces a further damage. The risk/benefit ratio of reperfusion depends on the amount of penumbral salvageable tissue, that is “individual” and only partially predictable.2,3 Spontaneous reperfusion may occur, and symptoms may reverse, partially or totally, but the percentages of spontaneous reperfusion so far reported account for approximately the 24% of all stroke cases.4 A review of published articles about cerebral angiography in stroke reported that the percentage of spontaneous reperfusion on a population of major strokes observed within 6 to 8 hours of onset is approximately 17% of patients.5

Pharmacological reperfusion is effective and recommended in selected cases.6 This population represents a minority of all hospitalized acute ischemic strokes; the majority of patients are excluded from the treatment because they present at the hospital over the 3-hour time window7–10. In this issue of Stroke, in the SAINT I and II trials pooled analysis, only 418 of 5080 acute ischemic stroke patients observed within 6 hours of stroke onset were reperfused.11 Sophisticated technologies have been introduced in order to select cases over the 3-hour time window at lower risk of reperfusion injury, with insufficient results on the number of treatable patients.12

Neuroprotective drugs can be potentially offered to a larger percentage of patients than thrombolysis. The expectation was that they will improve neurological function by supporting vital functions of ischemic brain cells, mainly through modulation of pathological ion transport over membranes, or else trapping free-radical agents inside the penumbra. Given the complexity of the maturation of ischemic damage, it is unlikely that a neuroprotective drug can counteract all the mechanisms involved in the cascade, irrespective to reperfusion, so as to definitely stop the process. Neuroprotection might slow down the cascade for a limited period of time, possibly enhancing the positive effects of reperfusion and/or reducing the reperfusion injury; in other words, they may widen the therapeutic window of thrombolysis, not reverse the penumbra in a sufficient number of cases to show a significant clinical effectiveness.

If it is so, the expected power of neuroprotective trial might be much lower than usually set, in particular lower than the power applied in the SAINT I and II trials.13,14

The SAINT II trial power was appropriately adjusted on the basis of SAINT I results. Why didn’t it work? The authors conclude that “The higher rate of alteplase use in SAINT I is unlikely to explain the different results in the two SAINT trials because there was no interaction between alteplase use and NXY-059 effect in either trial”. Maybe. But, the other possible explanation is that if the target is to show neuroprotection clinical effectiveness on the subgroup of patients that spontaneously reperfuse, even 5,080 patients might not be enough to show the drug effectiveness. Probably the clinical program for NXY-050, as well as for other neuroprotective drugs, has reached its conclusion as single-therapy. This is probably not the case for NXY-050 combined with thrombolysis, which might be able to enlarge the number of cases safely treatable with alteplase over the 3-hour time window.15

In the 1990s, combination trials have been suggested, designed, performed, and then abandoned.16–21 In 1998 the European Community funded a Multinational Project entitled “European Multicenter Four-Arm Trial in Acute Stroke-EMFATAS” BIOMED2 program contract No. BMH4-CT98-377, aimed at designing and conducting a four-arm combination trial in order to assess the safety and estimate the efficacy of neuroprotection plus rt-PA compared with neuroprotection alone, rt-PA alone and placebo.22

Unfortunately, at that time thrombolysis was not yet definitely approved, there were no evidences on the safety of any neuroprotective drug, methodology in clinical trial design was less sophisticated than now, and therefore the project was discontinued early.

Thrombolysis is now a routine treatment; some neuroprotective drugs have been demonstrated to be safe in both cerebral ischemia and hemorrhage, and an innovative methodological trial design has been introduced.23,24 Therefore,
thrombolysis plus neuroprotection combination trials seem today to be feasible.

The SAINT I and II trials pooled analysis results may be discouraging. A number of strokologists looked at the SAINT I results with hope, and we now are probably close to concluding that the potentiality of neuroprotection was unrealistic.

Is it really time to abandon neuroprotection in acute stroke clinical research, or are we just erroneously trying to reduce the number of steps needed to design an rt-PA plus neuroprotection combination trial model?

Disclosures

None.

References


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