Current Status of Neuroprotection for Cerebral Ischemia Synoptic Overview

Myron D. Ginsberg, MD

From the Department of Neurology, University of Miami Miller School of Medicine, Miami, Fla.

Abstract

Abundant preclinical studies have identified multiple mechanisms of ischemic brain injury and have provided proof of principle that strategies designed to counter these mechanisms can protect the ischemic brain. This review article emphasizes the translation of these strategies from the laboratory to clinical trials. It is a disappointing fact that many agents have been brought to clinical trial despite only modest or inconsistent preclinical evidence of neuroprotective efficacy. Preclinical investigations require rigorous attention to a variety of variables that may influence outcome. The widely touted STAIR criteria represent constructive guidelines for preclinical testing but, as experience has shown, do not increase the likelihood of translational success. Of the ≈160 clinical trials of neuroprotection for ischemic stroke conducted as of late 2007, only ≈40 represent larger-phase completed trials, and fully one half of the latter utilized a window to treatment of >6 hours, despite strong preclinical evidence that this delay exceeds the likely therapeutic window of efficacy in acute stroke. Other shortcomings of these trials include the use of agents lacking robust, consistent preclinical efficacy; inability to achieve adequate dosing in humans; and suboptimal clinical and statistical design features. Taken together, these factors identify areas of needed improvement for future trials.

Keywords

stroke; infarction; ischemia; neuroprotection; therapeutic window

Ischemic neuroprotection may be defined as any strategy, or combination of strategies, that antagonizes, interrupts, or slows the sequence of injurious biochemical and molecular events that, if left unchecked, would eventuate in irreversible ischemic injury. The author's recent extensive survey of neuroprotection for ischemic stroke, on which this overview is based, considers this topic in detail.[1]

A survey of MEDLINE-referenced publications[2] reveals virtually no publications on this theme until the early 1990s but an accelerating body of literature since then. In the period 2001 to 2007, >1000 experimental articles and >400 clinical articles have appeared on this topic. A vast body of experimental literature over several decades, however, has provided the pathophysiologic underpinnings of the neuroprotection field by virtue of systematic mechanistic studies of brain-injury pathophysiology in in vivo animal models and in vitro tissue

Correspondence to Myron D. Ginsberg, MD, Department of Neurology (D4-5), University of Miami Miller School of Medicine, PO Box 016960, Miami, FL 33101. E-mail E-mail: mginsberg@med.miami.edu.

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None.

preparations. These studies, taken together, have identified multiple injury-mechanisms, many of which represent potential targets of neuroprotective strategies (see Table 1 in Ginsberg[1]).

Despite the lack of successful clinical trials to date (see following paragraphs), experimental studies have provided incontrovertible proof of principle that it is possible to achieve high-grade (eg, >70–80%) reductions of ischemic brain injury by early neuroprotective interventions of a variety of types (cogent examples, some from the author's laboratory, include moderate hypothermia,[3] high-dose albumin,[4] radical spin trap,[5] and minocycline[6]). Nonetheless, it is certainly not the case that "everything works in animals." Many putatively protective agents eventually brought to clinical trial had shown, in point of fact, only modest or inconsistent tissue protection in preclinical studies. Of 66 such agents reviewed by O'Collins et al,[7] the mean extent of tissue protection observed in preclinical models was only 31±19%.

It is clear that preclinical (experimental) studies vary considerably in quality and reliability. A great number of variables come into play in the design and execution of these studies that influence their quality, consistency, and outcome. These variables comprise animal-related factors (species, strain, age, sex, comorbidities), anesthetic agents and drugs, extent and rigor of physiologic monitoring, animal model–related factors (choice of ischemia model; presence or absence of reperfusion; duration of ischemia, reperfusion, and survival), modes of outcome assessment, quality of statistical study design, and of course, the characteristics of the neuroprotective agent itself.

The preclinical STAIR criteria[8] represent constructive guidelines for preclinical testing, but adherence to these criteria has not proven to be predictive of eventual translational success. In a recent survey of 1026 neuroprotectant drugs or interventions for acute ischemia, as adherence to the STAIR criteria in these preclinical studies increased, the observed average level of neuroprotection (percent infarct volume reduction) tended to approach the mean value of the entire group of agents (25%, an arguably small and clinically unpromising level).[7]

When one surveys the universe of clinical trials of therapeutic strategies conducted to date in acute ischemic stroke (source: Internet Stroke Center, October 2007[9]), it becomes clear that antithrombotic and thrombolytic agents have been evaluated much more extensively than neuroprotectant agents themselves. A graphic synopsis of clinical neuroprotectant trials is shown in the Figure. In all, as of late 2007, ≈160 clinical trials of neuroprotection (excluding thrombolytic and antithrombotic agents) had been conducted in ischemic stroke.1 Of these, ≈40 were ongoing phase I, II, or III trials. There remain ≈120 trials that were taken to completion and for which interpretable information is available. Two thirds of these completed trials, however, were early-phase safety-feasibility trials of only 200 subjects or fewer (mean, 80±53). Thus, we are left with only ≈40 completed clinical trials of ischemic stroke carried out in >200 subjects. Of these larger completed trials, however, fully one half utilized a window to treatment of >6 hours (typically, 12, 24, or 48 hours after stroke onset). These long times to treatment are clearly incompatible with a consensus of preclinical evidence that neuroprotection is only possible within a narrow window of at most 4 to 6 hours after stroke onset. Indeed, even among the ≈19 larger trials with treatment windows of 4 to 6 hours, the overwhelming majority of these utilized a 6-hour window; as few as 2 such studies utilized windows <6 hours. Examples of the latter are shown in the Table. The implications of this table are clear: precious few large clinical neuroprotection trials have been conducted within the treatment window in which therapeutic efficacy is considered possible.

In addition to the use of treatment windows >4 to 6 hours, several other pervasive shortcomings are evident in the clinical neuroprotection trials conducted to date. These include (1) the use of agents that exhibited only weak preclinical neuroprotective efficacy (ie, <50%) or that were not robustly protective when administered at least 3 to 4 hours after stroke onset, or whose

preclinical efficacy was not consistently replicated; (2) the use of agents for which it was not possible to achieve preclinically efficacious doses or plasma levels in human subjects; and (3) the failure to incorporate crucial design features into pivotal clinical trials (eg, early time window to treatment initiation; adequate dosing; adequate follow-up period with meaningful primary outcomes; powering of sample size to demonstrate efficacy and avoid type II errors; and use of stratification variables relevant to the agent in question).

A final, crucial issue in clinical trials of neuroprotection is their mode of funding. It is clear that continued federal support will be crucial, particularly for trials involving nonproprietary agents and strategies (eg, magnesium,[10] albumin, [11] hypothermia). As has been cogently expressed in a recent review, "… drug development strategies adopted by the pharmaceutical industry are likely to address primarily commercial, regulatory, and marketing requirements rather than issues of public health."[12]

The topics assigned to the other authors of this section are intended to target key areas of current concern: (1) What lessons can a closer examination of the weakly positive SAINT I Trial[13] and the negative SAINT II Trial[14] of the antioxidant spin-trap agent NXY-059 teach us about translation of neuroprotectants from the bench to the bedside? (2) Which neuroprotective strategies targeting molecular modulators (eg, intracellular signaling molecules) appear most suitable for translation to human clinical trials? (3) What pharmaceutical industry impediments to the development of neuroprotective agents currently exist, and can promising agents be selected on the basis of knowledge of their molecular targets? And, finally, (4) what obstacles remain for the successful translation of therapeutic hypothermia to the clinic?

Acknowledgments

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Figure.
Clinical trials of neuroprotectants in acute ischemic stroke.[9] Reproduced with permission from Ginsberg MD. *Neuropharmacology*. 2008; Elsevier Publishing Co.

Table

Larger Completed and Published Randomized Clinical Trials of Neuroprotection in Acute Ischemic Stroke That Incorporate a Treatment Window of 6 Hours

Agent	Trial Name	No. of Subjects	Maximum Time to Treatment	Ref No.
Nimodipine	Very Early Nimodipine Use in Stroke (VENUS)	454	6 hours	15
Aptiganel	Aptiganel Acute Stroke Trial	628	6 hours	16
Selfotel	Acute Stroke Studies Involving Selfotel Treatment (ASSIST)	567	6 hours	17, 18
Gavestinel	Glycine Antagonist In Neuroprotection for patients with ischemic stroke (GAIN Americas)	1646	6 hours	19
Gavestinel	Glycine Antagonist (gavestinel) In Neuroprotection (GAIN International)	1804	6 hours	20
NXY-059	Stroke-Acute Ischemic NXY Treatment trial (SAINT I)	1722	6 hours	13
NXY-059	Stroke-Acute Ischemic NXY Treatment trial (SAINT II)	3195	6 hours	14
Tirilazad	RANdomized Trial of High-Dose Tirilazad in Acute Stroke (RANTTAS)	556	6 hours	21
Lubeluzole	US and Canadian Lubeluzole Ischemic Stroke Study	721	6 hours	22
Lubeluzole	European and Australian Lubeluzole Ischaemic Stroke Study	725	6 hours	23
Enlimomab	Enlimomab Acute Stroke Trial (EAST)	625	6 hours	24
UK-279,276	Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN)	966	6 hours	25