Perspectives on neuroprotective stroke therapy

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Abstract

After years of setbacks, the perspective of neuroprotective stroke therapy has revived in light of recent study results. We outline in this review how a neuroprotective candidate drug should be developed, beginning with a thorough preclinical evaluation according to the STAIR (Stroke Therapy Academic Industry Roundtable) criteria. Assessing the safety of the candidate drug in the relatively straightforward Phase IIA would be the first step into clinical development. While advancing into Phase IIB, the implementation of a responder analysis, the use of a surrogate biomarker as well as the use of Bayesian methodology should be considered to increase the likelihood of seeing any therapeutic sign. Clinical development in Phase III should consider that previously used dichotomized endpoints appropriate for evaluation of thrombolytic drugs are likely to be insufficient for assessing efficacy of neuroprotective drugs. Detection of a clinically relevant shift in the outcome measure appears to be a more relevant approach for the type of drug that achieves a reduction and not a reverse of the ischaemic lesion.

Despite several advantages in stroke care and therapy, only a small number of acute stroke patients (3%) receive specific therapy [1]. Sustained attempts to increase this percentage include the extension of the 3 h time window for intravenous thrombolysis by improving patient selection using DWI/PWI (diffusion- and perfusion-weighted imaging) [2]. Other strategies focus on the development of alternative thrombolytic agents such as demoteplase [3] with fewer side effects and a potentially wider time window, as well as the introduction of intra-arterial approaches [4]. In addition to vessel recanalizing strategies, research has focused on the introduction of neuroprotective pharmacological therapies. In a long history, potential neuroprotective drugs were evaluated in Phase II and III randomized multicentre clinical trials and until recently no successful candidates could be identified (for an overview, see Table 1). The reason for these devastating results is manifold and often includes the clinical trial design itself (see below). Other important reasons are related to the complex ischaemic pathophysiology as well as to side effects and the preclinical evaluation programme of the candidate drug.

By reviewing the long list of negative trials (see Table 1), it emerges that most drugs studied target only a single mechanism of ischaemic pathophysiology. Stroke, however, triggers an array of mechanisms, resulting in a complex cascade leading to the final infarction (see Figure 1). When a cerebral vessel is occluded, oxygen and glucose supply are disrupted, excitotoxic mechanisms become activated by an increase in extracellular glutamate concentrations, subsequently activating post-synaptic receptors, resulting in an intracellular calcium overload. The increased intracellular calcium subsequently rises due to secondary impairment of the Na/Ca exchanger. This secondary calcium increase is crucially toxic, causes overactivation of lipases, proteases and endonucleases and alters the function of receptors and membrane channels, that finally degrade the plasma membrane and the cytoskeleton. These processes then further induce and maintain mechanisms such as inflammation and apoptosis known to deteriorate cerebral ischaemia. Blocking just single mechanisms of this complex cascade by specific antagonists did not lead to an improvement in the stroke patients’ neurological outcome. Therefore a combination of differently acting drugs or drugs that exert multiple mechanisms of action, such as haemopoietic growth factors like erythropoietin or G-CSF (granulocyte colony-stimulating factor), could be promising to modulate or stop the dynamics of ischaemic pathophysiology and achieve synergistic effects [36,37]. Indeed, there is solid preclinical evidence indicating that combinations of neuroprotective agents synergistically decrease infarct volume, improve neurological outcome and extend the therapeutic time window [36]. Another important explanation for the lack of efficacy in human neuroprotective trials is the occurrence of dose-related side effects. It appeared that in humans adverse events of the studied drug occurred much more often compared with the preclinical experiments that were typically performed in rodents [38]. For example, as shown for glutamate antagonists, dose-escalation-limiting side effects occurred in humans with blood drug levels ranging well below the threshold shown in rodents to be neuroprotective. Furthermore, often insufficient preclinical evaluation of the candidate drug, without clarification of basic

Key words: clinical trial, neuroprotective drug, neuroprotection, stroke, thrombolysis, trial development

Abbreviations used: ASTIN, Acute Stroke Therapy by Inhibition of Neutrophils; CBF, cerebral blood flow; CBV, cerebral blood volume; CI, computed tomography; DWI, diffusion-weighted imaging; DWI/PWI, diffusion- and perfusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; mPA, recombinant tissue-type plasminogen activator; SAINT, Stroke–Acute Ischaemic NXY Treatment; STAIR, Stroke Therapy Academic Industry Roundtable.

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The early phases of clinical development, i.e. Phase I and Phase IIA, are straightforward. The neuroprotective drug should be evaluated for safety initially in healthy volunteers and then in stroke patients. For the Phase IIA study, it remains uncertain how many patients to assess per arm in a dose-escalation study. Typically, 12–15 patients are included per
Cerebral ischaemia triggers an array of mechanisms including depolarization of presynaptic neurons and glutamate release. By activating post-synaptic glutamate receptors intracellular calcium increases and activates pathological pathways such as apoptosis and release of toxic radicals maintained by intercurrent inflammation. The reorganization of the ischaemic and peri-ischaemic areas is triggered in the subacute phase post-stroke by recovery of enhancing factors, further inducing processes such as axo- and synapto-genesis. SVZ, subventricular zone.
clinical endpoints for acute stroke trials makes a typical Phase IIB neuroprotective trial severely underpowered for the detection of trends of efficacy, as these trials will usually include 100–200 patients per treatment arm. A potential solution for this dilemma is to use a relevant biomarker or surrogate marker in Phase IIB [42].

Currently, the best potential biomarker for a Phase IIB acute stroke, neuroprotective trial would appear to be MRI (magnetic resonance imaging). Diffusion MRI can determine the extent of ischaemic injury rapidly after stroke onset and can then be compared with lesion volume at a delayed time point on T2 or FLAIR (fluid-attenuated inversion recovery) imaging [43]. If the goal of neuroprotective therapy is to reduce infarct size as the mechanism that should translate into clinical benefit, then effecting ischaemic lesion growth or even promoting a reduction in the size of the ischaemic core would appear to be a relevant biomarker. Two approaches for evaluating the treatment effect on ischaemic lesions can be envisioned. One approach would be to compare the percentage increase in lesion volume from the pretreatment DWI (diffusion-weighted imaging) scan to the delayed day 30 or day 90 FLAIR lesion volume between the treated and placebo groups. Natural history studies suggest that ischaemic lesions will increase approx. 50–100% between these two time points, and a study containing 70–100 patients per treatment arm should be adequately powered [44,45]. Another approach would be to determine the percentage of patients who have no increase or shrinkage in lesion volume when the baseline DWI-determined lesion volume is compared with the delayed FLAIR volume, i.e. a responder analysis. The percentage of patients demonstrating such a pattern of no lesion growth or shrinkage is small without intervention. A two-stage approach to the Phase IIB trial can be employed [46]. In the first stage, two or more active treatment arms can be compared with the placebo arm. After a modest number of patients, the percentage of responders can be assessed, and if no or little difference is observed between one or more of the active treatment arms in comparison with the placebo arm, futility is determined. However, if one of the active treatment arms demonstrates the suggestion of an increase in responders, then enrolment in that arm and the placebo arm should continue in the second stage of the trial. Using this approach, 70–80 patients in both the active and placebo arms should be sufficient to detect a modest but statistically significant 20% increase in responders. If such an effect is observed, then it can be concluded that the neuroprotective drug under study does appear to have a biologically relevant effect on the evolution of ischaemic injury and a Phase III trial with a clinical endpoint should be performed.

Another important aspect of MRI-based Phase IIB trials is that the inclusion of relevant patients many hours from stroke onset can be targeted. This can be accomplished by looking for patients with a so-called ‘diffusion/perfusion (DWI/PWI) mismatch’ [47]. The region of abnormal perfusion with no diffusion lesion is likely to represent an approximation of the ischaemic penumbra, the target of acute neuroprotective therapy. Patients without such a mismatch are likely to have little or no penumbra. Preliminary evidence to support the utility of the mismatch concept for patient selection has begun to emerge. Case series of patients receiving intravenous rt-PA (recombinant tissue-type plasminogen activator) have shown that patients with a DWI/PWI mismatch between 3 and 6 h after stroke onset have a rate of favourable clinical outcome similar to patients treated in less than 3 h from stroke onset [49]. The recently reported DIAS (Desmoteplase In Acute ischaemic Stroke) and DEDAS (Dose Escalation study of Desmoteplase in Acute ischaemic Stroke) trials of the novel thrombolytic, desmoteplase, demonstrated a substantial treatment effect for improving clinical outcome in patients with a mismatch who were treated up to 9 h after stroke onset [3,50]. Thus, in a Phase IIB, MRI-based trial, the baseline imaging characteristics of individual patients can be used for inclusion/exclusion up to 9 h after stroke onset because a reasonable percentage of ischaemic stroke patients demonstrate a mismatch during this time period from stroke onset.

Perfusion CT (computed tomography) is another developing imaging modality that can provide an approximation of the ischaemic penumbra by evaluating relative CBF (cerebral blood flow) and CBV (cerebral blood volume) values [51]. In likely ischaemic regions with irreversible ischaemic injury, CBV collapses and absolute values are low. It has been suggested that ischaemic regions with reduced CBF values and CBV values that have not collapsed approximate the ischaemic penumbra. This CBF/CBV mismatch region could then be used to identify potential patients who are candidates for neuroprotective therapy hours after stroke onset in a manner similar to how the DWI/PWI is being employed in current clinical trials. Perfusion CT is an attractive alternative to advanced MRI because of the likelihood of greater availability of this advanced imaging technique as compared with MRI. However, several issues need to be addressed. The thresholds of CBF and CBV currently used with perfusion CT to identify abnormal regions are not validated and need to be further compared with DWI/PWI studies and PET (position emission tomography) studies. Making slight modifications in the CBV threshold used to define irreversible injury substantially impacts on the size of the purported penumbra. Another problem with perfusion CT is the limited spatial acquisition currently available [52]. Typically only two 5–10 mm slices can be imaged with the injection of one bolus of intravenous contrast. With a double injection, four such slices can be imaged. This does provide reasonable coverage of the middle cerebral artery territory, the region of stroke development most commonly affected in patients included in clinical trials. However, the relatively complete brain coverage afforded by DWI/PWI is not available. Another concern is that the natural history of a change in lesion volume on the baseline CBV study to a delayed infarct evaluated standard CT and has not been systematically studied. The effect of treatment on this evolution as an indicator of a treatment effect with a neuroprotective agent has not been evaluated in animal stroke models, as it has been in animal MRI studies. Currently, there are few case series reported that have used
perfusion CT to identify patients for delayed treatment, and the first clinical trials using this imaging modality for patient selection are only just beginning. The current concerns with perfusion CT are clearly surmountable and it is likely that it will be used widely in future neuroprotection trials, along with DWI/PWI.

Another approach to Phase IIB trial design is to use Bayesian methodology and decision theory to assign a greater percentage of patients to doses more likely to demonstrate benefit. Such an approach was utilized in the ASTIN (Acute Stroke Therapy by Inhibition of Neutrophils) trial of a polymorphonuclear leucocyte inhibitor [53]. In this study, the knowledge base was continually updated based on the actual outcomes of patients at different dose assignments in the trial, and assignment of patients was modified in response to this accruing information to assign more patients to more informative treatment arms. A clinical outcome measure, the Scandinavian Stroke Scale, was used to assess outcome and 16 different dose arms were included in the study. In the ASTIN trial, a stopping rule continuously ascertained if a particular dose had a <10% chance of success (futility) or a >90% chance of success. The trial ultimately did not show that any of the doses evaluated demonstrated a successful treatment effect, but the value of the trial is apparent as it showed that adaptive design trials can be performed with neuroprotective drugs. Refining the outcome measure used in adaptive design trial should be considered for future trials, such as using an MRI-based endpoint or a clinical endpoint adapted to baseline severity.

A neuroprotective drug demonstrating a reasonable treatment effect in an imaging-based or adaptive design-based clinical endpoint Phase IIB trial should then advance to a pivotal Phase III trial with a clinical endpoint. Until the recently presented SAINT (Stroke–Acute Ischaemic NXY Treatment)-I trial of the free radical scavenger NXY-059, the endpoints employed in all previous neuroprotective acute stroke therapy trials were dichotomous or trichotomous [29]. A typical approach was to define success as a statistically significant increase in the percentage of patients who achieved an mRS (modified Rankin Scale) score of 0–1 or 0–2 in the active treatment group as compared with the placebo group. Such an approach did show a statistically significant treatment effect in the NINDS rt-PA trial which dichotomized outcomes on the mRS, Barthel and NIHSS (National Institutes of Health Stroke Scale) were evaluated [29]. A robust treatment effect was observed in all three of these dichotomized outcome measures, driven by the 50% of patients in the trial in whom treatment was started within 90 min of stroke onset. Defining successful treatment as an mRS of 0–1, Barthel Index of 95–100 and/or an NIHSS of 0–1 essentially means that the patient has little or no functional, activity of daily living or neurological deficit, i.e. a ‘cure’ [54]. This may have been appropriate for rt-PA initiated within 3 h after stroke onset but it may not be the optimal way to evaluate more subtle but meaningful treatment effects likely to be engendered by neuroprotective agents or even delayed thrombolysis. A reanalysis of the NINDS rt-PA trial results by Saver [55] employing a novel assessment of treatment effect was performed. In this reanalysis, the effect of rt-PA treatment on the full range of mRS outcomes was evaluated. Essentially, in this type of analysis any shift of the mRS in a favourable direction is considered a favourable outcome. Using the full seven-category range of the mRS, the number of patients needed to be treated to improve by 1 grade or more was determined to be 3.1 (95% CI, 2.6–3.6), as compared with the number needed to be treated (8.4) if the mRS is dichotomized 0–2 or >2. Using the full range of the mRS to determine a ‘treatment effect’ that is clinically meaningful, as opposed to a ‘cure’, is an appropriate way to evaluate outcome for an acute stroke therapy. Looking for such a clinically meaningful treatment effect is relevant for neuroprotection because in animal studies a reduction of mean infarct size by 20–40% is considered a reasonable and statistically appropriate effect [38]. In stroke patients, such a neuroprotective drug should also reduce infarct size by some modest percentage and this reduction should then translate into clinical benefit as measured on an outcome scale such as the mRS. Shifting the mRS by 1 or more points will more likely capture the effect of treatment than would the dichotomized ‘cure’ approach used previously. In the SAINT-I trial, a shift in the mRS by 1 or more points was the primary outcome measure and it did show a statistically significant difference in the NXY-059 group as compared with the placebo group. No interaction of the treatment effect with rt-PA or time to treat was observed and the lack of these interactions is somewhat puzzling. A second NXY-059 trial, SAINT-II, is ongoing and the sample size was recently increased to add more power to the trial. The results are eagerly anticipated.

References

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