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Expert Opinion

Time for a neurorestorative therapy in stroke

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Stroke remains one of the main causes of death and disability worldwide. The aging of the population is likely to result in a dramatic increase in the burden of stroke. Thus, it is not surprising that the pharmaceutical industry has invested much money in the development of pharmacotherapies for ischemic stroke. Promising experimental data, however, have almost consistently failed to produce a clinically effective neuroprotective or neurorestorative drug. Only intravenous recombinant tissue plasminogen activator (rtPA) has been approved for the treatment of acute ischemic stroke. Many pharmaceutical companies have scaled down their stroke programs and despite the unmet need, activity in the field is almost frozen. Trafermin, a recombinant form of human basic fibroblast growth factor (bFGF), is a good example of a translational failure in neuroprotection. However, trafermin may also promote neuronal plasticity after cerebral insults. Thus, clinical trials with trafermin in stroke are warranted but should be based on neuronal restoration rather than acute neuroprotection.

Keywords: brain repair, neuronal restoration, neuroprotection, stroke, trafermin

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Effective pharmacotherapy for stroke remains an unmet need. Current research has primarily focused on prevention, acute recanalization and neuroprotection. Yet another approach is to enhance functional recovery. Together these provide complimentary strategies, with different mechanisms and therapeutic time windows that may help stroke patients (**Table 1**).

Preventative therapies, improved control of risk factors and lifestyle modifications are known to reduce stroke incidence and mortality [1]. Of the antiaggregants, aspirin leads to a 17–18% reduction in new stroke or transient ischemic attack (TIA) [2,3] and the combination of aspirin and slow release dipyridamole leads to a 38% reduction [3]. Furthermore, clopidogrel was shown to be as effective as the combination of aspirin and slow release dipyridamole in secondary prevention [4]. Low efficacy and bleeding complications have prompted the continued search for safer and more effective platelet antiaggregants. However, the testing of new treatments is becoming more difficult as shown by a large randomized trial of a novel antiplatelet agent, terutroban. This did not show any efficacy or safety advantages over aspirin for the secondary prevention of ischemic stroke or TIA [5].

Some bright light in stroke prevention comes from very recent anticoagulant trials. The Randomized Evaluation of Long term anticoagulant therapy (RE-LY) trial showed a reduction in stroke risk by a direct thrombin inhibitor, dabigatran (150 mg), compared with warfarin in patients who had atrial fibrillation, either with or without a history of stroke or TIA [6]. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, rivaroxaban, a factor Xa inhibitor, was shown to be equivalent to warfarin in patients with atrial fibrillation [7] and in the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial another factor Xa inhibitor,

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Table 1. Pharmacotherapy of stroke.

	Prevention	Neuroprotection	Neuronal restoration
Experimental models	A variety of thromboembolic models (e.g., $FeCl_3$, Rose Bengal induced)	A number of transient and permanent MCAO models	The MCAO models, emphasis on valid behavioral tests
Underlying neurobiological mechanisms	Multiple, well-understood	Multiple, well-understood	Multiple, knowledge is emerging on the brain's own repair mechanisms
Therapeutic time window	Before possible new or recurrent ischemic event	< 8 h	Days to months after ischemic event
Preclinical experience	Variable, mainly positive evidence	Huge number of positive experimental studies	Increasing amount of experimental evidence
Clinical experience	Reduction in major vascular events, bleeding complications	tPA, neuroprotective drugs not effective in patients so far	No proven therapy
Future hopes	Some progress expected	Activity in the field almost completely frozen	High

MCAO: Middle cerebral artery occlusion; tPA: Tissue plasminogen activator.

abixaban, showed superiority over warfarin in patients with atrial fibrillation in preventing stroke or systemic embolism and caused fewer bleeding complications [8].

Unfortunately, there is no effective drug therapy to help stroke patients during the acute phase except thrombolysis with recombinant tissue plasminogen activator (rtPA), which is only available for a small fraction of patients due to a narrow therapeutic time window of 4.5 h [9]. A number of trials are investigating how to extend the time window for thrombolysis or how to combine different therapies [10]. Alternative approaches for recanalization by using endovascular devices and techniques are also under development [11]. Neuroprotective drugs are effective in experimental settings, but despite huge efforts, none have so far worked in clinical practice [12,13]. The National Institutes for Health (NIH)-sponsored Albumin In Acute Stroke (ALIAS) Part 2 trial with albumin is one of the rare ongoing neuroprotective trials in stroke [14]. In addition, minocycline, magnesium sulfate and citicoline are currently being tested in Phase II and III clinical trials [13,15].

Another approach for the treatment of stroke is enhancement of spontaneous functional recovery. The adult brain is not as rigid as once thought and several repair mechanisms are activated in response to injury, including angiogenesis, neurogenesis and synaptogenesis [16,17]. More importantly, the brain repair processes can be further stimulated by rehabilitation, pharmacotherapy and cellular therapy. The major advantage compared with neuroprotection is the extended therapeutic time window up to several weeks or months after the initial insult. This makes the treatment available to a much larger number of stroke patients. In addition, different rehabilitative approaches can be combined to further boost functional improvement. For example, a recent study (Fluoxetine for Motor Recovery After Acute Ischemic Stroke (FLAME)) showed that early prescription of fluoxetine with physiotherapy enhances motor recovery after 3 months in patients with ischemic stroke [18].

Much hope and promise are placed on restorative therapies. Cell-based therapies, various growth factors, G-CSF and erythropoietin (EPO) are just a few potential strategies to enhance recovery processes [13,15]. In a recent issue of Expert Opinion on Biological Therapy, the clinical development of trafermin was summarized [19]. Promising experimental data with basic fibroblast growth factor (bFGF) were followed by Phase III patient studies at the acute phase of stroke, which failed to show neuroprotective effect and were perhaps prematurely terminated [20,21]. The previous experimental studies had included both permanent and transient middle cerebral artery occlusion (MCAO) models in several species, in line with the Stroke Therapy Academic Industry Roundtable (STAIR) recommendations [22]. However, at least two issues arise. Firstly, it was assumed that systemically administered bFGF crosses the damaged blood–brain barrier and is thus available to ischemic brain tissue. However, there were no proper dose–response studies in stroke animals regarding possible side effects. The intravenous doses for patient studies were scaled up according to body weight, resulting in adverse effects that led to the termination of the study. Perhaps the neuroprotective doses selected from animal studies were just too high. Also, the primary outcome measure was infarct size in most of the experimental studies. Additional use of predictive and sensitive sensorimotor and cognitive testing could have revealed a functional benefit in ischemic animals, which is more relevant to clinical practice.

Having a look back at the experimental data, it is now easy to second-guess that bFGF is restorative rather than neuroprotective. Chen *et al.* [23] suggested in 1994 that bFGF produced by neurons, macrophages and glial cells may enhance angiogenesis in MCAO rats. Later studies by Kawamata *et al.* [24,25] provided evidence that delayed administration of bFGF facilitates behavioral recovery after stroke, possibly through promoting new synapse formation, as indicated by growth-associated protein-43 (GAP-43) expression. Neurogenesis is also activated

by bFGF even in aged stroke rats, contributing to behavioral recovery [26]. To support this, Wang *et al.* [27] administered bFGF intranasally at several days after MCAO in rats and this enhanced neurogenesis and improved behavioral recovery. Interestingly, a *post-hoc* analysis of Phase III data revealed that the stroke patients who received 24-h infusion of bFGF at 5 h or later had improved clinical outcome, suggesting that treatment targeting the initial phases of brain repair may be beneficial.

Restorative therapies are integral in helping patients regain motor control after stroke. Based on both experimental data and subgroup analysis of clinical trials, a proof-of-concept study with bFGF is justified, but now with approaches that aim to enhance neuronal recovery and functional outcome in a carefully selected population of stroke patients. Previous experience and drawbacks should guide the clinical trial design, for example, intranasal administration of bFGF may be associated with fewer side effects [27], the combination of bFGF and intensive rehabilitative training and other restorative interventions might maximize the therapeutic benefit [28], and the use of appropriate functional endpoints might reveal the true functional recovery rather than compensatory strategies [29].

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

1. Sivenius J, Tuomilehto J, Immonen-Raiha P, et al. Continuous 15-year decrease in incidence and mortality of stroke in Finland: the FINSTROKE study. Stroke 2004;35:420-5
2. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;30:1849-60
3. Diener HC, Cunha L, Forbes C; European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1-13
4. Diener HC, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. Lancet Neurol 2008;7:875-84
5. Bousser MG, Amarenco P, Chamorro A, et al. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. Lancet 2011;377:2013-22
6. Diener HC, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol 2010;9:1157-63
7. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91
8. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92
9. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;3751:695-703
10. Amaro S, Chamorro A. Translational stroke research of the combination of thrombolysis and antioxidant therapy. Stroke 2011;42:1495-9
11. Jahan R, Vinuela F. Treatment of acute ischemic stroke: intravenous and endovascular therapies. Expert Rev Cardiovasc Ther 2009;7:375-87
12. O'Collins VE, Macleod MR, Donnan GA, et al. 1,026 experimental treatments in acute stroke. Ann Neurol 2006;59:467-77
13. Sahota P, Savitz S. Investigational therapies for ischemic stroke: neuroprotection and neurorecovery. Neurotherapeutics 2011;8:434-51
14. Ginsberg MD, Palesch YY, Martin RH, et al. The albumin in acute stroke (ALIAS) multicenter clinical trial: safety analysis of part 1 and rationale and design of part 2. Stroke 2011;42:119-27
15. Available from: www.clinicaltrials.com
16. Zhang ZG, Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. Lancet Neurol 2009;8:491-500
17. Font MA, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. Curr Cardiol Rev 2010;6:238-44
18. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol 2011;10:123-30
19. Paciaroni M, Bogousslavsky J. Trafermin for stroke recovery: is it time for another randomized clinical trial? Expert Opin Biol Ther 2011;11:1533-41
20. Clark WM, Wechsler LR, Sabounjian LA, Schwiderski UE; Citicoline Stroke Study Group. A phase III randomized efficacy trial of 2000 mg citicoline in acute ischemic stroke patients. Neurology 2001;57:1595-602
21. Bogousslavsky J, Victor SJ, Salinas EO, et al. Fiblast (trafermin) in acute stroke: results of the European-Australian Phase II/III safety and efficacy trial. Cerebrovasc Dis 2002;14:239-51
22. Stroke Therapy Academic Industry Roundtable. Recommendations for standards regarding preclinical neuroprotective and restorative drugs. Stroke 1999;30:2752-8
23. Chen HH, Chien CH, Liu HM. Correlation between angiogenesis and basic fibroblast growth factor expression in experimental brain infarct. Stroke 1994;25:1651-7
24. Kawamata T, Alexis NE, Dietrich WD, Finklestein SP. Intracisternal basic fibroblast growth factor (bFGF) enhances

behavioral recovery following focal cerebral infarction in the rat. J Cereb Blood Flow Metab 1996;16:542-7

25. Kawamata T, Dietrich WD, Schallert T, et al. Intracisternal basic fibroblast growth factor enhances functional recovery and up-regulates the expression of a molecular marker of neuronal sprouting following focal cerebral infarction. Proc Natl Acad Sci USA 1997;94:8179-84
26. Won SJ, Xie L, Kim SH, et al. Influence of age on the response to fibroblast growth factor-2 treatment in a rat model of stroke. Brain Res 2006;1123:237-44
27. Wang ZL, Cheng SM, Ma MM, et al. Intranasally delivered bFGF enhances neurogenesis in adult rats following cerebral ischemia. Neurosci Lett 2008;446:30-5
28. Matsuse D, Kitada M, Ogura F, et al. Combined transplantation of bone marrow stromal cell-derived neural progenitor cells with a collagen sponge and basic fibroblast growth factor releasing microspheres enhances recovery after cerebral ischemia in rats. Tissue Eng Part A 2011;17:1993-2004
29. Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensation" mean in patients following stroke? Neurorehabil Neural Repair 2009;23:313-19

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