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STROKE IN 2012

Major advances in the treatment of stroke

Miguel Blanco and José Castillo

Several clinical trials and experimental studies that could have a major impact on the treatment of patients with ischaemic stroke were published in 2012. The studies cover all therapeutic options, including stroke prevention, recanalization and thrombolysis, neuroprotection, and promising new therapeutic approaches focused on neurorepair.

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Despite improvements in its management in recent years, cerebrovascular disease remains a major cause of mortality and morbidity. The current framework of therapeutic options to prevent or treat stroke comprises a spectrum of five fields of treatment—primary prevention, recanalization and thrombolysis, neuroprotection, secondary prevention, and neurorepair (Figure 1). In 2012, we witnessed developments in all five areas, with important implications for stroke treatment.

When primary prevention fails, an effective protocol for acute stroke treatment is imperative, early reperfusion of ischaemic tissue being the primary goal. Currently, thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) is the most effective approach. However, the extensive exclusion criteria, together with the short therapeutic window and narrow age range, severely restrict its use. The Third International Stroke Trial (IST-3)[1] was conducted to establish the balance between benefits and harms of rtPA treatment in patients who did not accomplish the licence criteria and, hence, to determine whether a wider range of patients might benefit up from rtPA up to 6 h from stroke onset.

IST-3 enrolled 3,035 patients (1,515 in the rtPA group and 1,520 controls), 53% of whom were aged >80 years. No differences were found between groups with respect to the primary end point (37% in the rtPA group versus 35% of controls survived and achieved independence). The global benefits of rtPA treatment seemed to be greatest within the first 3 h from stroke onset, but the analyses had insufficient power to define the benefit in a therapeutic window beyond 3 h. Interestingly, treatment efficacy was similar between patients older and younger than 80 years. The IST-3 data reinforce the need for further efforts to increase the proportion of ischaemic strokes treated within 3 h, but they provide reassurance that rtPA treatment in elderly patients and within 6 h from stroke onset does not increase mortality.

Although clinical trials with neuroprotective agents have systematically failed, neuroprotection remains a treatment option for acute ischaemic stroke. In 2012, the results of ICTUS (International Citicoline Trial on acUte Stroke) were published.[2] In this trial, patients with moderate to severe acute ischaemic stroke were treated with either citicoline or placebo within 24 h after symptom onset. The primary outcome was recovery at 90 days measured by a global test combining three measures—NIH Stroke Scale score ≤1, Modified Rankin Scale score ≤1, and Barthel Index score ≥95—in accordance with a pooled meta-analysis of previous randomized trials with citicoline.[3]

2,298 patients (1,148 assigned to citicoline and 1,150 to placebo) were enrolled in ICTUS.[2] Global recovery was similar in both groups, and no significant differences were reported in the safety variables or the rate of adverse events. Although ICTUS followed a protocol nearly identical to that of the pooled meta-analysis,[3] with minimal differences in statistical analysis, none of the benefits for citicoline were confirmed. However, the previous clinical trials with citicoline were conducted 10 years ago, and the standard of stroke care has substantially improved in the meantime. Also, the patients in ICTUS were, on average, 4 years older, and were over three times more likely to have received rtPA treatment, than those in previous trials. Comparison with the older studies suggests that the benefits of citicoline have become diluted in parallel with improvements in the standard of care for acute ischaemic stroke—a fact that should be taken into account for future trials of neuroprotective drugs.

To initiate appropriate secondary prevention, it is essential to know the cause of stroke, yet at least one-quarter of strokes are still classified as cryptogenic. The ASSERT investigators recruited 2,580 individuals >60 years without a history of atrial fibrillation (AF) in whom a pacemaker or defibrillator had been implanted.[4] Patients were

monitored for 3 months to detect subclinical atrial tachyarrhythmias (ATs; episodes of atrial rate >190 bpm for >6 min), and were followed up for a mean of 2.5 years for the primary outcome of ischaemic stroke or systemic embolism. At least one AT was detected in 10.1% of patients. During the follow-up period, 4.2% of patients in whom subclinical AT had been detected had an ischaemic stroke or systemic embolism, compared with 1.7% in whom subclinical AT was not detected. The attributable risk of ischaemic stroke or systemic embolism associated with subclinical AT was 13%, which is similar to the stroke risk associated with AF.[5] On the basis of these results, AT must be considered as a new source of embolism in patients with cryptogenic stroke.

The prevalence of patent foramen ovale (PFO) ranges from 20–26% in the general population, but may be as high as 56% in patients under 55 years who have experienced a cryptogenic stroke.[6] The CLOSURE I investigators evaluated the potential benefits of percutaneous device closure versus medical therapy for secondary stroke prevention in patients with PFO.[7] This multicentre, randomized, open-label trial compared PFO closure (using the STARFlex device) with medical therapy (warfarin, aspirin or both) in patients 18–60 years of age with PFO who had presented with cryptogenic stroke or TIA within the previous 6 months. The primary end point was a composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurological causes between 31 days and 2 years.

909 patients—447 percutaneous device and 462 medical therapy—were enrolled. At 2 years, effective closure was maintained in 86.7% of cases. The incidence of the primary end point was 5.5% in the percutaneous device group and 6.8% in the medical group. Stroke incidence was 2.9% in the percutaneous device group and 3.1% in the medical group. No deaths occurred by 30 days in either group, and there were no deaths from neurological causes during the 2-year follow-up period. AF was significantly more frequent in the closure group (5.7% versus 0.7%). In conclusion, closure did not offer greater benefits than medical therapy alone for the prevention of recurrent stroke or TIA.

Over the past two decades, stem cell-based neurorepair has emerged as a promising therapeutic option for ischaemic stroke. Animal experimental data with embryonic stem (ES) cells, neural progenitor cells or bone marrow-derived progenitor cells are encouraging; however, no proven stem cell-based therapy is currently available for stroke. Despite the supposed immunoprivileged status of the CNS, allogeneic grafts of stem cell-derived neurons and glia remain susceptible to rejection. A novel alternative strategy to avoid graft rejection and immunosuppression is to generate induced pluripotent stem cells (iPSCs) from somatic cells.

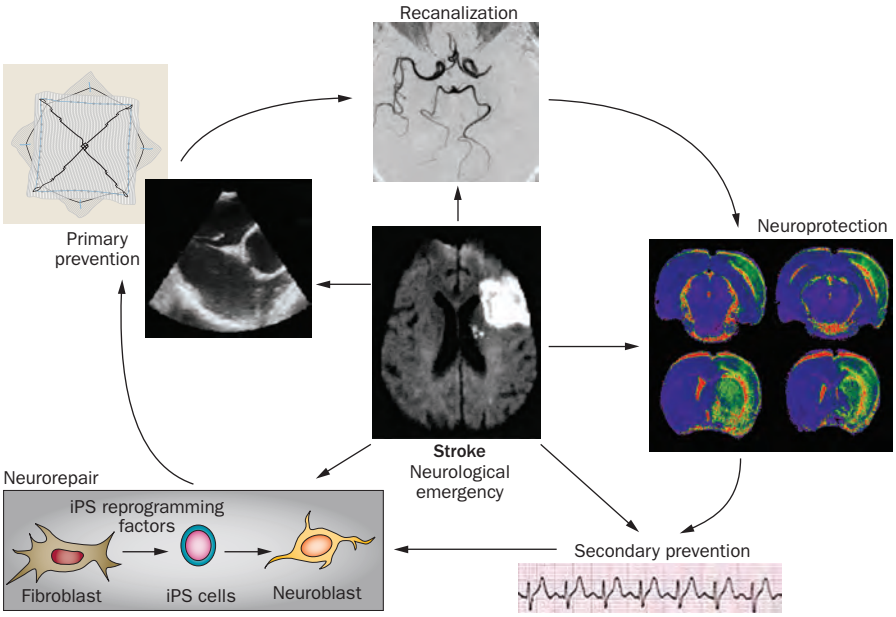

Figure 1 | Spectrum of therapeutic options to prevent or treat stroke. In 2012, key advances were made in stroke prevention (primary and secondary), recanalization and thrombolysis, neuroprotection, and neurorepair strategies. Abbreviation: iPS, induced pluripotent stem.

In 2006, it was reported that skin fibroblasts from adult mice could be reprogrammed to a pluripotent state by retroviral expression of four transcription factors.[8] The resulting iPSCs are indistinguishable from ES cells in morphology, proliferative capacities, surface antigens, gene expression, epigenetic status, and telomerase activity. The Nobel Prize in Physiology or Medicine 2012 was awarded to Sir John B. Gurdon and Shinya Yamanaka for this breakthrough.

The Laboratory of Neural Stem Cell Biology and Therapy, Lund, Sweden transplanted long-term self-renewing neuroepithelial-like stem cells, generated from adult human fibroblast-derived iPSCs, into stroke-damaged mouse and rat striatum or cortex.[9] The transplanted cells stopped proliferating, could survive without forming tumours for at least 4 months, and differentiated into morphologically mature neurons. Grafted cells exhibited electrophysiological properties of mature neurons and received synaptic input from host neurons. Most importantly, recovery of forepaw movements was observed by 1 week after transplantation. This study provides the first evidence that transplantation of human iPSC-derived cells is a safe and efficient approach to promote repair and recovery after stroke.

The advances described above reflect progress across the spectrum of therapeutic options in stroke, from primary prevention to neurorepair (Figure 1). Every step takes us towards the ultimate aim of better outcomes and quality of life for patients with stroke.

Key advances

- IST-3 reinforces the need for further efforts to increase the proportion of ischaemic strokes treated within 3 h, but provides reassurance that thrombolysis in elderly patients or within 6 h from stroke onset does not increase mortality[1]
- Under the conditions of the ICTUS trial, citicoline is not effective in the treatment of moderate to severe acute ischaemic stroke[2]
- Atrial tachyarrhythmia must be considered as a new source of embolism in patients with cryptogenic stroke[4]
- Patent foramen ovale closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA[7]
- An animal study provides the first evidence that transplantation of cells derived from human induced pluripotent stem cells is a safe and efficient approach to promote recovery after stroke[9]

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J. Castillo declares an association with the following company: Ferrer Grupo. See the article online for full details of the relationship. M. Blanco declares no competing interests.

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MOVEMENT DISORDERS IN 2012

Advancing research towards novel therapeutic approaches

Nikolaus R. McFarland and Michael S. Okun

Research in movement disorders in 2012 has improved our understanding of the pathogenic mechanisms of disease and led to development of potential novel therapeutic approaches. Key advances were linked to mechanisms underlying spread of neurodegenerative pathology, immunotherapy, stem cells, genetics and deep brain stimulation in parkinsonism and related disorders.

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Despite recent advances in our understanding of the pathogenesis and treatment of movement disorders such as Parkinson disease (PD), many of these syndromes remain challenging to diagnose and to treat. Moreover, disease-modifying therapies remain elusive. Continued progress in elucidating the pathophysiology of these disorders and translation of research from bench to bedside will result in better diagnostics and development of novel therapeutics. Research in 2012 has moved the field closer to this goal, and important progress had been made in numerous areas, including basic and clinical work in parkinsonism, dystonia, Huntington disease (HD), essential tremor, and tic disorders. We highlight some of the recent and key advances in each area that are collectively leading to improved understanding of basic pathophysiology and novel approaches to therapy.

A major hallmark of PD and related disorders is the presence of Lewy body pathology, with concomitant neurodegeneration linked to abnormal accumulation and deposition of α-synuclein. Mounting evidence supports the hypothesis of prion-like spread of pathology via cell-to-cell transmission of pathological forms of proteins such as α-synuclein.[1] Unanswered questions remain, however, about the mode of transmission of pathological α-synuclein species and their role in disease pathogenesis.

Building on previous work demonstrating the ability of preformed α-synuclein fibrils to precipitate Lewy body-like pathology and neurodegeneration, Luk and colleagues recently showed that intracerebral injections of exogenous preformed fibrils or brain homogenates from old, symptomatic Ala53Thr transgenic mice (which express Ala53Thr human α-synuclein) into younger, asymptomatic mice could accelerate Lewy pathology.[2] In the inoculated animals, widespread α-synuclein pathology—including misfolded and hyperphosphorylated α-synuclein and intracellular Lewy-like inclusions—was observed, with a resultant decrease in survival of these animals. The findings provide further evidence of prion-like spread and propagation of synucleinopathy, and cell-to-cell transmission of pathological proteins. Furthermore, exogenous preformed α-synuclein fibrils were sufficient to produce this cascade of events and accelerate the disease phenotype *in vivo*. On the basis of these findings, targeting of cell-to-cell transmission to block the spread of synucleinopathy is a promising therapeutic approach to disorders such as PD.

Evidence points to an important role for release of extracellular α-synuclein from neurons in the transmission of pathology. Approaches such as passive and active immunization to target α-synuclein have shown promise in synucleinopathy models, with reduction in α-synuclein accumulation and associated neurodegeneration.[3,4] The exact mechanism of action, however, remains unclear. In a study published in *The Journal of Neuroscience*, Bae *et al.* hypothesized that antibodies against α-synuclein target extracellular α-synuclein and aid microglia in the clearance of pathological protein species, thereby preventing cell-to-cell propagation of pathology.[5] The researchers showed that α-synuclein antibodies bound to extracellular aggregates are taken up by microglia through surface Fcγ receptors, and are then delivered to microglial lysosomes for degradation. Intracerebral injection of α-synuclein antibody in a transgenic mouse model also resulted in α-synuclein clearance, and specifically reduced neuron-to-astroglia transmission of the protein, promoting microglial uptake and removal of extracellular α-synuclein. These studies help to further elucidate the mechanism of cell-to-cell transmission of α-synuclein, and highlight a potential immunotherapy for PD and related disorders.

Advances in other synucleinopathies such multiple system atrophy (MSA)—a disorder in which standard PD therapies often fail—have also been made. Following an initial open-label trial of autologous mesenchymal stem cells (MSCs) in MSA that attracted criticism from researchers in the field but also provided hope for a novel therapy, Lee *et al.* reported the results of a 1-year randomized clinical trial.[6] The therapeutic mechanism