

controversial hypotheses of AD pathogenesis. The first is the amyloid hypothesis, which still has many advocates despite the recent failures of the first two anti-amyloid drugs (tramiprostate and tarenflurbil) to complete phase III studies. The second, and arguably more controversial hypothesis, relates to the role of metal ions in AD. Because many factors affect the accumulation of A $\beta$ , whether the attenuation of the interactions of metal ions with A $\beta$  will be sufficient to alter the course of AD is uncertain. If we assume that the amyloid hypothesis holds water, future clinical studies with PBT2 will not only test the mettle of MPACs but also provide the first real-world test of the importance of metal ion homeostasis in the pathogenesis of AD.

*Norman R Relkin*

Director, Memory Disorders Program, Weill Cornell, Medical College, New York, NY  
nrelkin@med.cornell.edu

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<http://www.myriad.com/news/release/1170283>

## “Telethrombolysis”: stroke consultation by telemedicine



With only 40% of intravenous alteplase-treated patients having no handicap 3 months after stroke, compared with 25% placebo-treated patients, it is clear that this therapy is not the panacea of stroke treatment.<sup>1</sup> However, in addition to stroke unit care, it is the most effective treatment so far, and every eligible patient should be given the opportunity of treatment.<sup>2,3</sup> The implementation of alteplase treatment that follows recommendations has been very slow.<sup>2,3</sup> The main obstacles include the strict 3 h time window from symptom onset and that the diagnosis of acute stroke and the decision to give alteplase treatment are delicate, thus limiting the use of alteplase to trained stroke physicians. In 2007, fewer than 1500 patients in France received alteplase treatment after stroke despite the fact that 150 000 strokes are estimated to occur each year (Amarenco P, unpublished). In Germany or the USA, it is estimated that only up to 5% of patients can be treated.

Although many patients and their relatives still do not respond appropriately to the symptoms of an acute ischaemic attack because of lack of awareness, many others simply live too far away from a stroke unit, even if helicopter transfer facilities are available. This creates a dichotomy of care for stroke management: one for fortunate patients who are located sufficiently close to a stroke unit to arrive within the 3 h therapeutic window, and another for patients who are unable to present quickly enough to benefit from alteplase treatment. In this issue of *The Lancet Neurology*, Meyer and colleagues report on delocalising stroke expertise with telephone or video conferencing consultation.<sup>4</sup> This trial randomised

222 patients presenting with symptoms of stroke in a remote hospital. Video conferencing (ie, telemedicine) was shown to be more accurate than telephone consultation when making decisions with regard to thrombolytic treatment.<sup>4</sup> In this study, there was an imbalance at baseline in the National Institutes of Health stroke scale (NIHSS) for between-group mean score (11.4 $\pm$ 8.7 in the video conferencing arm and 7.7 $\pm$ 7.0 in the telephone arm,  $p=0.002$ ). Among the 222 patients randomised (111 in each arm), 56 received thrombolytic therapy with a mean baseline NIHSS score of 14.5 $\pm$ 7.2; there was also an imbalance between the groups who received thrombolysis (16.3 $\pm$ 7.4 in the telemedicine arm and 12.3 $\pm$ 6.3 in the telephone arm;  $p=0.04$ ). Overall, a correct treatment decision (as adjudicated by an independent committee) was made in 98% ( $n=108$ ) of patients randomised to video conferencing and in 82% ( $n=91$ ) of patients randomised to telephone ( $p=0.0009$ ), but the 90-day functional outcomes were similar for the Barthel index and modified Rankin scale. However, neither video conferencing nor telephone consultation was shown to be equivalent to the gold standard of immediate transfer of eligible patients to a stroke unit for alteplase therapy given by a trained stroke physician. This might not be possible to test in remote hospitals that are located too far away to allow transfer to a stroke unit, even by helicopter, as was the case for many centres in the study reported by Meyer and colleagues. In such cases, it would be beneficial to know whether telephone consultation would be better than no telephone consultation, with a cluster randomised

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trial design. Another shortcoming of the trial was that the design was not restricted to the 3 h time window, which makes the correct decision-making results speculative compared with current guidelines and recommendations. Because agreement in correct decision making was likely to be very high between both arms after 3 h, the steering committee thought that the trial might be underpowered, and decided to halt it after blind analysis showed a 0.96–0.99 probability that one arm was superior to the other. Finally, although recruitment of 400 patients was planned, only 222 were randomised, and—together with the significant imbalance in baseline NIHSS—this small sample size resulted in low power of the study to look for a substantial difference in the 90-day outcome, even in a secondary analysis. Therefore, there are uncertainties about the generalisability of the study.

Remote, rural and suburban hospitals commonly do not have a stroke physician, or even a neurologist. Patients with stroke who are admitted to these hospitals are not usually considered for alteplase therapy, even if they are eligible. Some patients are transferred to a stroke unit, but eligible patients commonly miss the 3 h time window because of the duration of transfer, or are treated close to 3 h even though they should have been treated much earlier (“Time is brain: each minute lost is 2 million neurons lost”).

In cardiology, the number of patients with an acute coronary syndrome who are being prescribed alteplase therapy has increased because the involvement of emergency medicine physicians has increased. In the stroke field, although senior emergency medicine physicians can diagnose most strokes and select eligible patients for alteplase therapy—and then follow the recommended procedures—some physicians who are less familiar with stroke diagnosis and treatment could benefit from the video conferencing system for supervision by a senior vascular neurologist. Diagnoses of posterior circulation stroke or basilar artery occlusions commonly need very specialised skills. In these circumstances, video conferencing with stroke experts might help emergency medicine physicians in diagnosis and triage, and in selecting the most appropriate treatment (eg, intravenous alteplase or endovascular treatment).

This trial by Meyer and colleagues does not provide definitive evidence for the use of telemedicine. Although video conferencing is appealing and seems intuitively effective in remote decision making for thrombolytic

treatment in acute stroke<sup>6</sup>, there are many problems to consider, such as incorrect application of recommended procedures by the remote emergency medicine physician and the scarcity of stroke-unit facilities in the remote hospitals, which decreases the likelihood of recovery. Therefore video conferencing-assisted thrombolysis (or “telethrombolysis”) in patients with stroke will remain at evidence level IIb<sup>2</sup> (level Ia is the highest grade of evidence in the European Stroke Organisation).<sup>2</sup>

Many experiences of the “telestroke” network have been launched with some success since 1998 and their results have been reassuring.<sup>7–10</sup> For example, during the second year of the telemedic pilot project for integrative stroke care (TEMPiS) programme in Bavaria, 2.4% (115 of 4727) of patients with a stroke or transient ischaemic attack who were admitted to one of the 12 community hospitals and underwent telemedicine consultation received intravenous alteplase.<sup>11</sup> A further 5.8% (110 of 1889) of patients admitted to the two academic stroke centres (the “hubs” of the TEMPiS network) received systemic thrombolysis. The rate of in-hospital mortality was low (3.5% vs 4.5%, respectively), and the rate of symptomatic intracerebral haemorrhage was not statistically different (7.8% vs 2.7%, respectively). As shown by Audebert and co-workers, a 42% relative risk reduction in poor outcome (adjusted odds ratio 0.62, 95% CI 0.52–0.74;  $p < 0.0001$ ) in patients with acute cerebrovascular syndrome was seen in networked hospitals compared with those admitted to control hospitals without telemedicine facilities.<sup>12</sup> Telemedicine consultation can be reasonably used when transfer to a stroke centre is not possible. This telemedicine strategy is a level IIb recommendation from the European Stroke Organisation.<sup>2</sup>

The next step is to show that telethrombolysis is equivalent to or better than the gold standard treatment to improve the percentage of patients with no handicap at 3 months. This would represent level Ia evidence for using and developing telemedicine for equal and improved access to thrombolytic treatment in all patients with stroke. Such a study is currently recruiting patients in France: the telemedicine for remote collaboration with urgentists for stroke—tPA treatment trial (TRUST—tPA; registered with ClinicalTrials.gov, number NCT00279149).<sup>13</sup> In the meantime, the study by Meyer and colleagues reinforces the point that telethrombolysis should be preferred to telephone consultation.

**Pierre Amarenco**

INSERM U-698, Clinical Research in Atherothrombosis and Denis Diderot University, Paris VII, Bichat Stroke Centre, Paris, France  
 pierre.amarenco@bch.aphp.fr

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## Neutralisation of IL12 p40 or IL23 p40 does not block inflammation in multiple sclerosis



Crohn's disease, psoriasis, rheumatoid arthritis (RA), and multiple sclerosis (MS) are deemed to be autoimmune diseases that develop in genetically predisposed individuals.<sup>1</sup> CD4+, Th1, and Th17 T-cell populations have been seen as main factors in the pathogenesis of MS, on the basis of the strong genetic association of certain HLA-class II molecules with MS, immunological findings in the animal model of experimental autoimmune encephalomyelitis (EAE), and in patients with MS.<sup>1</sup> However, several immune cells—including CD8+ T cells, dendritic cells (DC), natural killer cells, and B cells—and soluble mediators, such as autoantibodies, cytokines, and chemokines, all have important roles, with varying effects, at different stages of the disease.<sup>1</sup>

A range of immunomodulatory drugs are currently in development for relapsing-remitting MS, including oral compounds and monoclonal antibodies that target specific receptors or molecules that are thought to be crucial for the pathogenesis of MS. Among the latter, the cytokines IL12 and IL23 are of particular interest because they have central roles in the differentiation of the two main proinflammatory CD4+ T-cell populations: Th1 cells and Th17 cells. IL12 and IL23 are heterodimers that have a common subunit (p40) and have either p35 (IL12) or p19 (IL23) as a second subunit.<sup>2</sup> IL12 and IL23 are produced by myeloid cells and bind to receptors that are expressed on T cells. IL12 signaling is thought crucial for Th1

differentiation, and IL23 signaling for the differentiation and maintenance of Th17 cells.<sup>3</sup> Both IL12 p40 and IL23 p40 have been detected in MS lesions, and mononuclear cells in patients with MS have increased concentrations compared with controls. The neutralisation of IL12 p40 or IL23 p40 inhibits EAE in rodents and non-human primates.<sup>4</sup> Furthermore, mice that are genetically deficient in IL12 p40 and IL23 p19 are resistant to EAE.<sup>5</sup> Thus, there is strong evidence that blocking IL12 p40 or IL23 p40 would be beneficial to patients with MS.

Contrary to this expectation, Segal and co-workers,<sup>6</sup> in this issue of *The Lancet Neurology*, show that different doses of ustekinumab, an antibody that neutralises IL12 p40 and IL23 p40, do not inhibit disease activity in patients with relapsing-remitting MS. 249 patients were treated with four different dosing regimens of ustekinumab or placebo for 19 weeks. A sensitive readout—the cumulative number of contrast-enhancing cranial MRI lesions—was chosen, and there was no difference from placebo in the ustekinumab treatment arms.

The authors offer several explanations as to what went wrong. They posit that ustekinumab might not have crossed the blood brain barrier, or that crucial events in T-helper cell differentiation had occurred much earlier during the course of the disease and were not affected by inhibition of IL12 p40 or IL23 p40. The assumption that treatment might have come too late is unlikely because

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