Report

□ International Stroke Trial 3

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In May 2012, the results of the Third International Stroke Trial (IST-3) were published in the Lancet. The study was coordinated by the University of Edinburgh and conducted between May 2000 and July 2011. The trial compared thrombolytic therapy with intravenous recombinant tissue Plasminogen Activator (rt-PA) *vs*. placebo in acute ischaemic stroke patients to investigate the effect of the treatment, administered within 6 hours of symptom onset, in adult patients of all ages. The pre-specified sample size was 3,100 patients, and with this sample, a 4% difference in primary outcome was noted.

IST-3 was an international, no-profit, multicentre, randomized-controlled, open-treatment, blind end-point assessment trial (PROBE). Randomization of participants was conducted by telephone or by a secure web-based randomization system. Participating hospitals, spanning 12 countries, had to have an organized system of stroke care in place. Patients were allocated either for immediate thrombolysis with 0.9 mg/kg of i.v. rt-PA to a maximum of 90 mg, or to a control group, given aspirin immediately. Blood pressure was managed in the same way in both treatment groups, following the local protocol in use. CT or MRI scans of the brain were required before randomization and after 24-48 hours. All CT/MRI scans were sent to the trial centre in Edinburgh to be scrutinized by an international panel of expert radiologists, blind to the treatment.

The primary outcome was the proportion of patients alive and independent, as defined by an Oxford Handicap Score (OHS), a variant of the modified Rankin score, of 0-2 at 6 months. While the study was ongoing, a secondary outcome was introduced to take into account new evidence regarding a favourable prognosis (European Cooperative Acute Stroke Study: ECASS3), namely the proportion of patients with an OHS of 0-1 at 6 months. Ordinal analysis of the OHS scores at 6 months completed the ordinal shift analysis and evaluated all movements of a single OHS level to produce a global odds ratio, as this analysis is today considered the most sensitive and powerful means of highlighting differences in treatment efficacy.

3,035 adult acute ischaemic stroke patients of all ages, scanned via cranial CT or MRI and treated within 6 hours of onset, were enrolled in a total of 156 centres across 12 countries. Exclusion criteria were intracranial haemorrhage, structural brain lesions and contraindications for rt-PA treatment. Patients with a slim chance of benefiting from treatment were also excluded, i.e., those manifesting blood pressure and glucose levels outside protocol definitions (< 54 mg/dl or > 360 mg/dl) and those with previous ischaemic stroke or fibrinolytic treatment within the previous 14 days.

The exclusion criteria adopted were less restrictive

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Progress in Neuroscience 2013; 1 (1-4): 7-9. *ISSN: 2240-5127*
Article received: 15 April 2013. doi: 10.14588/PiN.2013.Sicilia.7

than those specified under the Italian Ministerial license for rt-PA, which are: age under 80, treatment within 3 hours of onset of symptoms (4.5 hours in Europe), NIHSS < 25, CT or MRI scan with absence of any visible signs of early ischaemia, no previous ischaemic stroke or diabetes, and no other standard exclusion criteria. Indeed, 95% of the patients enrolled (2,581) in our study were off-label according to current licensing standards for rt-PA treatment, and did not meet the EU-licence-approval criteria. In particular, only 28% of the sample was randomized within 3 hours of onset (the mean time from onset to treatment was 4.2 hours), 53% (1617 patients) were older than 80 years of age, and 43% had experienced extensive stroke (Total Anterior Circulation Infarct: TACI).

Here for the first time, the statistical analysis plan was published before the results were known, and included the most up-to-date and accurate techniques available, such us ordinal shift analysis. At 6 months, 37% (554/1,515 patients) in the rt-PA group, *vs*. 35% (534/1,520 patients) in the control group, were alive and independent (OHR 0-2). The absolute difference between the two, i.e., 14 additional patients per 1,000 treated (95% Confidence Interval: CI 20/48) was not significant. The percentage of patients with a favourable prognosis at 6 months was, however, significantly increased, at p = 0.018 with an odds ratio of 1.26 (CI 1.04/1.53). Indeed, 29 additional patients per 1,000 treated displayed an OHS score of 0-1. Shift analysis of the distribution of OHS scores at 6 months revealed odds of survival with less disability > 27% in the rt-PA group (p = 0.001, 95% CI 1.10/1.47).

Fatal intracranial haemorrhages occurred within 7 days in more patients in the rt-PA group (7%, 104/1,515 patients) than in the control group (1%, 16/1,520). This percentage of 7% is the same as the 7.3% cited in the SITS register (Safe Implementation of Thrombolysis in Stroke) in 6,483 patients treated according to EU-licence-approval criteria, if the Cochrane definition of SICH (Symptomatic Intra-Cranial Haemorrhage) is applied. Furthermore, more deaths occurred within 7 days (163 patients, 11%) in the rt-PA group than in the control group (107 patients, 7%), but between from 7 days and 6 months there were fewer deaths in the rt-PA group (244 patients, 16%) than in control patients (300 patients, 20%). Mortality at 6 months was comparable in both groups: 27% (408/407). Subgroup analyses, adjusted for age, treatment onset and clinical syndrome stroke severity, provided evidence of a favourable primary outcome and greater benefit in patients treated within 3 hours, those above 80 years of age, and those with severe stroke.

To summarize, at 6 months the absolute effects per 1,000 patients treated by rt-PA were:

- 14 more patients alive and independent (not significant), 29 more patients with favourable prognosis (p = 0.018), increased survival with less disability (favourable shift in OHS p = 0.001) and similar mortality in patients of all ages when treatment was administered within 6 hours.
- 38 more patients above 80 years of age were alive and independent when treated within 6 hours.
- 80 more patients, younger and older, were alive and independent when treated within 3 hours.

For the type of patients recruited in IST-3, despite the early hazards, thrombolysis within 6 hours improved functional outcome, but the greatest benefit was seen in patients treated within 3 hours. This benefit does not seem to be diminished in elderly patients and those with more severe stroke.

IST-3 data were incorporated into a systematic Cochrane review of 12 trials on thrombolysis with intravenous rt-PA for acute ischaemic stroke, totalling 7,012 patients. Early outcome (within 7 days) and late outcome (at the end of follow-up between 7 days and 6 months) were considered for patients treated within 6 hours, as well as outcomes according to treatment time after onset and related to age and treatment time. This analysis showed that:

- spontaneous intracranial haemorrhage (SICH) is the sole greatest cause of early risk:
- few patients treated with rt-PA treatment died between 7 days and the end of follow-up;
- rt-PA had no effect on total deaths by the end of follow-up;
- a greater benefit was seen in patients treated within 3 hours;
- patients treated between 3 and 6 hours after stroke onset may benefit;
- the benefit experienced by younger patients and those older than 80 years was comparable, especially if treated within 3 hours.

Implications for clinical practice:

- The effects of the treatment reported in IST-3 on this wide range of patients were consistent, with particular relative benefit noted in patients older than 80 years of age and those with severe stroke, so rt-PA treatment appears to be a viable option in this population.
- These results reinforce the need to increase the

number of ischaemic stroke patients treated within 3 hours.
- This type of treatment does not increase mortality.

Implications for research:
- IST-3 data provides the rationale for the ongoing trials of thrombolysis in patients presenting more than 4.5 hours after onset of stroke.
- It is difficult to justify future trials with upper age limits in acute stroke.
- Additional subgroup data (single patient meta-analysis) is required to identify predictive features of benefits and harms.

In conclusion we can say, in total agreement with Charlotte Cordonnier and Didier Leys, that IST-3 must change our approach to the acute ischaemic stroke patient, since it "is now our role not to identify patients who will be given rt-PA, but to identify the few who will not."

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