Final report summary:

Early, clot-busting stroke treatment: is a newer drug more effective than the drug currently used?

Alteplase-Tenecteplase trial evaluation for stroke thrombolysis (ATTEST) – pilot phase
Early, clot-busting stroke treatment: is a newer drug more effective than the drug currently used?

There is only one treatment currently available for the acute treatment of stroke, called thrombolysis. It is the injection and intravenous administration of the clot-busting drug alteplase within 4.5 hours of stroke onset to help break down the clot, and return blood flow to the brain to reduce brain damage. This treatment has remained unchanged since 1995.

Tenecteplase is a newer drug that has already superseded alteplase in the treatment of heart attacks (myocardial infarction). It has a number of improved properties over alteplase in that it can be given via injection,

Around 85% of strokes are caused by a blood clot blocking an artery (“ischaemic stroke”). Brain tissue is starved of oxygen and nutrients, and unless the blood supply is restored quickly, the tissue supplied by the blocked vessel will die.

Treatment with drugs to break down clots (thrombolysis, or “clot-busting” treatment) increases the chances of opening the blocked artery and restoring blood flow. If given very early after the onset of symptoms (currently up to a maximum of 4.5 hours), clot-busting drug treatment significantly increases the probability of someone regaining independence after the stroke.

Tenecteplase has several advantages over alteplase. Tenecteplase is easier to administer, as it consists of a single injection compared to a combination of part dose injection then intravenous infusion over one hour; it persists for longer in the circulation and may therefore open blocked arteries more effectively; it also binds to clots more specifically, and should therefore have lower risks of bleeding. These properties led to it replacing alteplase and other older drugs for treatment of heart attacks (myocardial infarcts) some years ago.

The ATTEST pilot study compared tenecteplase with standard alteplase treatment in acute ischaemic stroke patients, in a prospective randomised, controlled (computed tomography) brain imaging to provide more information about how the treatments were working and explore whether there were differences between them: CT perfusion (measuring brain blood flow) to assess the extent of brain tissue at risk, and CT angiography (visualising blood vessels) to assess which blood vessel was involved, and whether a blockage was successfully cleared. The findings of this study provided information that will be crucial in designing a future large clinical trial to compare the two drugs.

Patients with acute stroke who were eligible for treatment with alteplase were recruited to the trial at the acute stroke service at the Institute of Neurological Sciences in Glasgow. Treatment was allocated randomly via a computer system, and participants received either standard alteplase, or tenecteplase, commenced as early as possible after having a CT scan. Follow-up scans were performed at 24 hours, and clinical checks on progress were made at several time points, with a final determination of outcome at 3 months after the stroke using a standard scale of disability, the modified Rankin Scale. Between January 2012 and September 2013, 104 patients were recruited, 52 patients in each group: 96 patients with confirmed stroke were included in the final analysis.
What did the researchers find?

The participants were typical of people included in acute stroke trials. The two groups were well balanced for clinical characteristics such as age, gender, co-morbidities (the presence of one or more additional disorders), stroke onset to treatment time, and stroke severity. However the research scans revealed some potentially important differences in that more people assigned tenecteplase had a blockage affecting a very large artery (74%), compared to those who received alteplase (61%), and the amount of irreversibly damaged tissue pre-treatment was greater in the tenecteplase group. Overall, the researchers found no difference between the treatments in the amount of brain tissue that was rescued, the final size of the strokes, or the success at opening blood vessels, and although more people in the tenecteplase group recovered fully by 90 days (28% compared to 21%), this was not statistically significant.

However, there was a trend towards more patients treated with tenecteplase improving neurologically at 24 hours (40% compared to 25%); and of potential importance, the overall brain haemorrhage rate was lower in the tenecteplase treated group (14% compared to 29%), although there were too few brain haemorrhages that potentially caused worsening of someone’s condition to see a clear difference (2% compared to 4%).

In conclusion, tenecteplase is a promising treatment for stroke with potential advantages. Even if it is no different in terms of effectiveness compared to our current standard drug, it is easier and quicker to give and less expensive, and the trial suggests that it may also be safer. Given that the group allocated to tenecteplase treatment had a greater chance of unsuccessful treatment and more bleeding since their strokes involved larger blockages and more irreversibly damaged tissue, it is worthwhile testing tenecteplase in a larger clinical trial to see if it can improve outcomes.

In February 2015, the findings from this study were published in the journal, The Lancet Neurology.

A proposal for the study will be submitted to the Medical Research Council (MRC).

What does this mean for stroke survivors?

Tenecteplase may prove to be a superior drug to alteplase for the treatment of acute ischaemic stroke. Even if tenecteplase itself is no more effective, or safer than alteplase, it could still offer valuable time saved as it is easier and quicker to administer to stroke patients.

As time saved is brain saved in the crucial minutes following a stroke, this one benefit alone could lead to an improved likelihood of patients regaining long term independence.

Alteplase is currently the only drug licensed for the treatment of ischaemic stroke by thrombolysis.
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