Can an anti-inflammatory drug reduce damaging inflammation after ischaemic stroke?

Final report summary:

Does subcutaneous interleukin-1 receptor antagonist reduce inflammation after ischaemic stroke compared to placebo?

PROJECT CODE: TSA 2012-08
PRINCIPAL INVESTIGATOR: PROFESSOR CRAIG SMITH
INSTITUTION: UNIVERSITY OF MANCHESTER
Why did we fund this research?

Ischaemic strokes account for about 85% of all strokes\(^1\). They are caused by a blocked artery in the brain, usually by a blood clot. Apart from aspirin, the only drug treatment we currently have to treat ischaemic stroke is thrombolysis, which uses clot-busting drugs to dissolve the clot and can lead to an improved recovery for many patients. However, less than 12% of stroke patients in the UK are currently eligible to receive thrombolysis and it carries some risks, including bleeding in the brain\(^2,3\).

A haemorrhagic stroke is caused by a bleed within (intracerebral haemorrhage) or on the surface of the brain (subarachnoid haemorrhage). It accounts for about 15% of all strokes\(^1\). Thrombolysis cannot be given to haemorrhagic stroke patients, and there is currently no emergency drug treatment for it.

It is therefore clear that new treatments are needed to improve the likelihood of all stroke patients having a better outcome after stroke, and which can also be used alongside thrombolysis in patients eligible for that proven treatment.

One area of investigation has been into the inflammation in the brain that follows a stroke. Inflammation is triggered by the body’s immune system to help defend it against infection or damage. Following injury, proteins called cytokines are released at the site of damage and also into the blood stream, acting as a signal to initiate repair and healing. Despite inflammation being a natural response to injury, it can also go into overdrive, and cause further damage under some circumstances, including after a stroke.

Pre-clinical, animal research suggests that in the early period after stroke there are abnormally high levels of inflammation in both the blood and brain, and that higher levels of inflammation in the blood are associated with more severe disability and an increased risk of death after stroke too\(^4,5\).

An artificial version of IL-1Ra, called anakinra, is also currently licensed as a treatment for some inflammatory conditions including rheumatoid arthritis. Anakinra has already been used in a number of studies of ischaemic and haemorrhagic stroke in which the drug was found to be well tolerated and safe to use with patients\(^7,8\).

One of the main proteins in the body associated with inflammation after stroke is called interleukin-1 (IL-1) which is naturally blocked in the body by the production of another protein called ‘interleukin-1 receptor antagonist’ (IL-1Ra). Pre-clinical research has shown that IL-1Ra can significantly reduce brain injury after stroke\(^4,5,6\).

The main aim of this research was to test whether anakinra, given as injections under the skin, could reduce levels of inflammation after ischaemic stroke compared to placebo (dummy drug) in a clinical trial. A second aim was to see whether patient disability was reduced three months after stroke in those treated with anakinra.

If the main results of the trial were found to be positive, it was hoped larger trials could follow to establish whether treatment with anakinra could reduce disability or death after ischaemic stroke.

(Further clinical trials are separately investigating whether anakinra could be used to treat intracerebral haemorrhage and subarachnoid haemorrhage\(^8\).)
What did the researchers do?

Eighty participants were recruited to take part in the trial from the Greater Manchester Comprehensive Stroke Centre. All participants had an ischaemic stroke within five hours of being recruited to the study, which did not interfere with or delay their clinical care. The average age of participants was 72, and 73% of all participants received thrombolysis as part of their clinical care.

Half of the participants were randomly assigned to receive treatment with anakinra, and the other half to a placebo (dummy drug). Participants received six 100mg doses of either anakinra or placebo, both given as an injection into the skin. The first dose started within six hours of their stroke symptom onset, and then again at least six hours after the first dose and continued every 12 hours until completion of the six doses.

Neither the participants, nor the researchers knew whether the participant had been given Kineret or placebo (double blinded study). Both groups underwent the same blood sampling and daily clinical assessments at 7am on the following three days after their stroke. Blood samples were analysed in the lab to look for key signs of inflammation after stroke (inflammatory markers).

Three months after their stroke participants (or their next of kin) were contacted and asked for information about their recovery. This was measured using a standard questionnaire called the modified Rankin Scale (mRS), which is commonly used by doctors to assess recovery after stroke.

What did the research find?

Of the 80 participants recruited to the trial, 63 had sufficient blood samples obtained to be included in the final analysis (28 participants from the anakinra group and 35 from the placebo group).

The main research question was answered: patients who received anakinra had significantly reduced levels of inflammatory markers (called IL-6 and CRP) in their blood when compared to the placebo group. These markers are associated with a worse outcome after ischaemic stroke and are known to be induced by the protein IL-1, which is blocked by anakinra. Such a robust reduction in these inflammatory markers has not yet been demonstrated with any other candidate anti-inflammatory drug for acute ischaemic stroke.

Nevertheless, it was also found that participants in the anakinra and placebo groups had similar levels of disability at three months after stroke, as indicated on the modified Rankin Scale (mRS). This finding was unexpected and contrasts with a similar anakinra trial in subarachnoid haemorrhage by the same research group. That trial did suggest an improved recovery with anakinra, and the research has now progressed on to a definitive trial to test the effectiveness of anakinra in subarachnoid haemorrhage.

A possible reason anakinra did not affect participant outcome at three months after stroke is that the trial was too small to detect a difference. However, this trial is the first of its kind where anakinra has been tested in stroke patients alongside their treatment with thrombolysis. The thrombolysis drug ‘alteplase’ could interact with anakinra which could plausibly reduce its effectiveness in reducing brain injury after stroke. This question should be fully investigated in further studies of anakinra in the presence of thrombolytic drugs such as alteplase.

The full findings of this trial were published in March 2018 in the journal Stroke.

What does this mean for stroke patients?

The anti-inflammatory drug IL-1ra (anakinra) is a promising drug that may be able to improve outcomes for ischaemic stroke patients in the future. However, further studies are needed, including investigation of how IL-1Ra interacts with the clot-busting drug treatment, thrombolysis.
References


We are the Stroke Association

The Stroke Association is the leading stroke charity in the UK. We believe in the power of research to save lives, prevent stroke and ensure that people make the best recovery they can after a stroke.

We’re here for you. If you’d like to know more, please get in touch.

**Stroke Helpline:** 0303 3033 100  
**Website:** stroke.org.uk  
**Email:** info@stroke.org.uk  
**From a textphone:** 18001 0303 3033 100

Our research programme relies on voluntary donations.

Please help us to fund more vital research.

Call our Donations line on **0300 3300740**, or visit **stroke.org.uk**

Together we can conquer stroke