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NEWS

Researchers say they will send unpublished alteplase data to UK drug regulator on request

Deborah Cohen, Helen Macdonald

The BMJ

Previously unpublished data that could potentially resolve concerns over the safety and efficacy of the acute ischaemic stroke drug alteplase will be made available to the UK drug regulator on request, an email seen by *The BMJ* has indicated.

Alteplase is the only thrombolytic drug with a licence for the management of acute ischaemic stroke. In some countries in Europe, including the United Kingdom, it is marketed for use within four and a half hours of onset of symptoms, and in the United States it is marketed for use within three hours.

However, the use of alteplase has been shrouded in controversy almost since the drug was approved (1996 in the US and 2002 in parts of Europe), with some doctors and academics questioning its efficacy and safety and the methodology of some of the trials.

In August 2014 the UK Medicines and Healthcare Products Regulatory Agency (MHRA) convened a group of experts to review "any new information or concerns about the data that underpin the present marketing authorisation" of alteplase,[1] after a letter in the *Lancet* raised concerns about the evidence on which the licence was based.[2] However, when it announced the review the MHRA believed that the data had been "extensively discussed" and that the "benefit-risk balance is favourable."

But Roger Shinton, author of the *Lancet* letter and a former consultant physician at Birmingham's Heartlands Hospital, said that it had become clear that "decisions about treatment require a fuller picture than is currently available." Doctors needed to know the effect of the drug when used at different times after onset of symptoms, in different age groups, and in patients of varying stroke severity, he said.

"Current uncertainty means the full picture is needed. This picture should include residual symptoms, disability, all bleeding events, allergic reactions, brain scans, final place of residence, and, of course, mortality patterns," he said. Many of these data from trials were not currently publicly available, he added.

Shinton said that the trials had more objective endpoints that were not in the public domain and that would help understand the clinical uses of the drug.

At the first of the MHRA meetings in November 2014 Shinton said that he had urged the regulator to ask for any unpublished data to enable full understanding of the safety and efficacy of alteplase.

In October 2014 Shinton had written to Colin Baigent, professor of epidemiology at Oxford University's Clinical Trials Support Unit and corresponding author of an individual patient data meta-analysis of alteplase, published in the Lancet in August 2014,[3] to request further data. The meta-analysis was conducted by the Stroke Thrombolysis Trialists' Collaborative Group, funded by the UK Medical Research Council, British Heart Foundation, University of Glasgow, and University of Edinburgh. It included the key trials used to support the use of the drug.

"The recent *Lancet* individual patient data meta-analysis appears to have provided a carefully crafted optimistic impression of benefit," Shinton said. Well recognised and emerging problems with the original trials have not been made completely clear, he added. He also called into question whether the individual patient data meta-analyses should have included more sensitivity analyses and also other trials that had been excluded. Had this been done, perhaps the analysis would have drawn more cautious conclusions, he said.

Baigent did not give Shinton the additional data he had asked for but said in an email to him that he agreed that "the best evidence should be made available to inform patients, professionals and regulators." Baigent added that "it would be preferable for such evidence to be provided by the STT [Stroke Thrombolysis Trialists] to the [MHRA's] expert group as a whole. As such we will consider any requests for additional analyses that come from the expert group chair after having considered representations from all interested parties."

The BMJ asked Baigent if he was willing to make further data available to the MHRA if the agency asked for the data and why he declined to give Shinton further data to help him resolve his concerns—concerns that Shinton said were shared by other medical staff. Baigent told *The BMJ*, "As a member of the expert group reviewing alteplase for acute stroke on behalf of the MHRA, I am explicitly bound to keep all business related to this review confidential. In light of this, I do not think it is appropriate for me to comment."

The BMJ also put to Baigent the methodological criticisms raised by Shinton. He has not responded directly to these.

Shinton has also asked the MHRA to reanalyse the data so that age and baseline stroke severity could be fully accounted for in assessments of the drug's efficacy.

So far the MHRA has not made the terms of reference, the scope, or the composition of the review committee public, despite telling The BMJ that it would do so when it announced the review last year. The MHRA's committee is set to meet again later this month.

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The BMJ has also learnt that the House of Commons Health Committee will hold a session with the MHRA once the outcome of the review is known, which will be early this year. The committee has said that it wants to have a chance to look at the alteplase issue before the end of the current parliament.

1 Cohen D, Macdonald H. UK drug agency announces review of use of alteplase after stroke. *BMJ* 2014;349:g5355.

2 Shinton R. Questions about authorisation of alteplase for ischaemic stroke. *Lancet* 2014:384:659-60.

3 Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014:384:1929-35.

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