Summary of the conclusions of the Expert Working Group of the Commission on Human Medicines on alteplase

Background

Alteplase is a so-called 'clot-busting' drug which is used in the treatment of heart attacks, blood clots in the lung, and acute ischaemic stroke (an interruption of blood supply to the brain caused by a blockage). It acts by breaking down blood clots, allowing blood flow in the affected vessel to resume. Although alteplase can benefit patients by restoring blood flow to areas of the brain that have been affected by stroke, thereby improving outcome, the treatment also carries the risk of bleeding into the brain (intracranial haemorrhage, ICH), which can be serious and in some cases is fatal. This risk is kept to a minimum by careful brain imaging to make sure that the stroke is due to a blood vessel blockage rather than a bleed.

The Expert Working Group

An Expert Working Group (EWG) of the UK Commission on Human Medicines (CHM) was formed to consider the latest data on the benefit and risk of alteplase in stroke. The Group, chaired by Professor Sir Ian Weller, included members with expertise in neurology, cardiology, emergency medicine, statistics, epidemiology and patient representation and with a broad range of experience. The Group's conclusions and recommendations have been carefully considered and fully endorsed by the CHM.

Data that supported the Product Licence

Evidence relating to alteplase treatment in acute ischaemic stroke has increased substantially since its use in stroke was first approved in the UK in 2003. At the time of approval, our understanding of the beneficial and harmful effects of alteplase was mainly based on data from six clinical trials (called NINDS parts 1 and 2[1], ECASS I[2] and II[3], and ATLANTIS A[4] and B[5]). The design of these trials differed from each other in many aspects including, most importantly: the time-window in which alteplase treatment was given to patients after the onset of a stroke; the dose given; and the patient outcomes studied. Although these factors complicate evaluation of the results, these trials enabled a suitable dose of alteplase to be selected and a population to be defined for whom it was felt the benefit of treatment outweighed the risk. At the time of licensing in 2003, the time-window for administration of alteplase was restricted to up to 3 hours from the onset of stroke symptoms.

Since then, another trial called ECASS III[6] has completed. This trial, together with reassuring data from observational studies (in particular the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry, SITS-ISTR[7]) and a pooled analysis of clinical trial data, led to the conclusion in 2012 that the chance of a good outcome with alteplase treatment outweighed the risk of an ICH when it was given up to 4.5 hours after the onset of stroke.

Recent data

More recently a large study, the third international stroke (IST-3) trial[8,9], has provided a substantial amount of helpful information, particularly on the types of patients that have not previously been well represented in clinical trials (e.g. patients over the age of 80 years, or those with a severe stroke). Further observational data, including analyses from the SITS registry (SITS-ISTR[10] and SITS-UTMOST), the Get With The Guidelines-Stroke registry from the US[11], and the Baden-

Wuerttemberg Stroke registry from Germany[12], have also provided reassuring data to support the safe use of alteplase in the clinic.

In 2014, the Stroke Thrombolysis Trialists' (STT) Collaborative Group published a meta-analysis which is the largest, most up-to-date body of data on the benefit and risk of alteplase[13]. This meta-analysis assimilated individual patient data from nine clinical trials (the eight trials mentioned above plus the EPITHET trial) involving a total of 6756 patients. It showed that alteplase demonstrated significant benefit after 3 to 6 months, with about 10% more patients (10 in every 100) being disability-free when treated within 3 hours, and about 5% more patients (5 in every 100) being disability-free when treated between 3 and 4.5 hours after the onset of symptoms compared with patients who do not receive alteplase. As expected, alteplase also increased the risk of bleeding in the brain soon after treatment, equivalent to a 2% (2 in 100 patients) increase in fatal events. The EWG considered this meta-analysis to be a rigorous and reliable evaluation of the available clinical trial data on use of alteplase in stroke.

Data considered by the EWG

The EWG considered information from a range of sources, presented in a series of papers. These included: the published literature, data from the marketing authorisation holder, submissions from clinicians and professional bodies, additional analyses from the Stroke Thrombolysis Trialists' Collaborative group, information from the National Reporting and Learning System, the Sentinel Stroke National Audit Programme (SSNAP) and the stroke guidelines.

The Group reviewed the findings from a large number of studies, including all those mentioned above. They also considered carefully specific concerns that had been raised by some physicians on the data supporting the use of alteplase. These concerns included: the design and conduct of trials (including for example, the choice of outcomes studied, how patients were randomised to treatment in the trials, how patients and professions involved in the trials were blinded to the treatment allocation); the analyses of the results (such as the impact of baseline imbalances in stroke severity and other characteristics between the two arms of the trials, the pattern of times from stroke onset to treatment, and possible impact of recall bias); the applicability of the results to other patients; and the appropriateness of the way the results have been presented in medical literature. After careful consideration of every issue, the EWG concluded that none provided evidence to alter the conclusion that the benefit-risk balance of alteplase treatment was positive.

To help with their review of the evidence, the EWG asked the STT Collaborative Group to do some further analyses of their data. These included removing the NINDS trials from the meta-analysis, because it was suggested that these data were skewing the results, and expressing the results using different definitions of a 'good outcome'. The EWG considered that these further (unpublished) analyses reinforced the overall findings of the meta-analysis in confirming that the benefit of alteplase outweighs the risk within 4.5 hours of symptom onset.

The EWG also considered in detail the effect of: time from onset of stroke symptoms to treatment; baseline stroke severity; and patient age on the balance of benefit and risk. The Group then considered whether any measures were necessary to further improve the benefit risk balance of alteplase in stroke. The Group concluded that the balance of benefit and risk changes with time to treatment, with the risk of ICH remaining the same and the benefit becoming smaller with increasing time to treatment. It was considered that the effectiveness of alteplase when given within 4.5 hours of stroke onset did not vary according to stroke severity or age (<80 or ≥80 years).

Clinical use of alteplase in the UK

The EWG also considered the current clinical use of alteplase in the UK and the practicalities of its use within the terms of the SmPC. It also looked to see how frequently the use of alteplase was associated with medication errors, whether other illnesses or other medicines patients may be taking affected alteplase treatment, and whether there are any measures that should be taken to further minimise any risk to patients.

The EWG was reassured about the way alteplase is being used in the UK, and where medication errors had been reported they mainly related to dosing and administration. The EWG advised that provision of a weight-based dosing table to physicians and some minor clarifications of the instructions for administration could be helpful.

Communication of benefit and risk to patients and their families

The Group discussed the challenges of explaining the benefit and risk of alteplase treatment to patients and their families or carers at the time of a stroke, and they considered the strategies which had been found to be most successful. The Group noted that speaking with the patient and family or carer was most important, and that while patients and family wanted to be guided in their decision regarding treatment, there was evidence to suggest that they generally also wanted the physician to make the ultimate decision on whether or not to give alteplase. The EWG concluded that it is important that healthcare professionals are given the tools and information they need to better understand the available data and therefore be confident in their decisions and advice for patients. The Group concluded that further evaluation of the available support materials (in addition to the SmPC and patient leaflet) would be helpful.

Overall conclusions and recommendations

The CHM endorsed the overall conclusions of the EWG as follows:

- the data that have become available since 2012, when the time-window for treatment with alteplase was increased to 4.5 hours after onset of symptoms, add substantially to the understanding of the evidence on which the current marketing authorisation is underpinned and the balance of benefit and risk of alteplase over time and in different patient populations
- the benefit of alteplase in the treatment of stroke outweighs the risk when used in accordance with the product licence—ie, up to 4.5 hours after symptom onset
- the benefit of alteplase in the treatment of stroke is highly time-dependent and therefore minimising the time to onset of treatment is critical to ensuring the best possible outcome

The details of the data evaluated by the EWG and CHM, and the minutes from the EWG meetings are available on GOV.UK.

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