Alteplase

Essential medicine status

Section: 12. Cardiovascular medicines > 12.5. Antithrombotic medicines > 12.5.2. Thrombolytic medicines

ATC codes: B01AD02

Indication	Cerebral ischaemic stroke ICD11 code: 8B11
INN	Alteplase
Medicine type	Chemical agent
List type	Complementary
Formulations	Parenteral > General injections > IV: 10 mg in vial powder for injection ; 20 mg in vial powder for injection ; 50 mg in vial powder for injection
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Alteplase
DrugBank	Alteplase

Expert Committee recommendation

The Committee recommended the addition of alteplase on the complementary list of the EML as a thrombolytic agent for use in patients diagnosed with acute ischaemic stroke on the basis of the evidence presented of improved patient outcomes in terms of reduced death or dependence when alteplase is administered within 4.5 hours of the onset of stroke symptoms. The Committee acknowledged the significant global burden of stroke in terms of death and disability, and particularly in low- and middle-income countries. The Committee noted that optimal use of alteplase would require timely and highly organized care pathways, in facilities that are equipped and capable of managing stroke patients.

Background

The application requested the inclusion of alteplase on the complementary list of the EML as a thrombolytic agent for use in patients diagnosed with acute ischaemic stroke (AIS) with a potentially handicapping neurological deficit at the time of thrombolysis, and treatment within 4.5 hours after onset of stroke symptoms (or after last proof of good health if unknown onset of symptoms). Alteplase had not been previously considered for inclusion on the EML.

Public health relevance

Globally, stroke is the second leading cause of death and disability, with the bulk of the burden (almost 80%) residing in low- and middle-income countries (LMICs) (1, 2). In 2016, there were almost 14 million new cases of stroke, 5.5 million deaths associated with stroke and about 81 million stroke survivors. 30% of strokes are fatal in the first year and a further 70% of survivors are left with some level of disability. Although stroke incidence, mortality and disability burden rates have declined since 1990, in 2016 the absolute number of people who died from stroke, remained disabled from stroke, were affected by stroke (as measured by incidence of new strokes), or survived stroke had almost doubled largely due to aging of the population and population growth (2). In well a well-developed stroke system, about 25% of all AIS patients who arrive to a stroke centre within 24 hours of last proof of usual

health are eligible for intravenous thrombolysis (3). In Europe the current true rate is only 7.3% for all AIS patients (4), in the United States this number is probably similar (5). Very few patients in LMICs receive intravenous thrombolysis (6, 7).

Benefits

A 2014 Cochrane systematic review of 27 trials involving 10 187 participants assessed the effectiveness and safety of thrombolytic therapy for treatment of acute ischaemic stroke (AIS) (8). Ten trials in the review assessed alteplase in 6886 participants. Compared to control, intravenous alteplase administered within 6 hours, was associated with a significant reduction in death or dependence (odds ratio (OR) 0.84, 95%CI 0.77 to 0.93, p=0.0006), corresponding to death or dependence in 40 fewer participants per 1000 treated (95%CI 20 fewer to 65 fewer). When a random-effects model analysis was performed due to the significant heterogeneity of treatment effect among the trials, the OR was 0.80 (95%CI 0.66 to 0.97, p=0.03). For participants receiving alteplase within 3 hours (6 trials, 1779 participants), there was a significant reduction in death or dependence compared to control (59.3% vs 68.3%; OR 0.65, 95%CI 0.54 to 0.80, p<0.0001), with no significant heterogeneity, corresponding to death or dependence in 90 fewer participants per 1000 treated (95%CI 46 to 135). There was a non-significant reduction of death in the long-term follow up of patients treated within 3 hours with an OR of 0.91 (95%CI 0.73 to 1.13, p=0.39), with no statistically significant heterogeneity (p=0.22) and 14 fewer per 1000 deaths (95%CI 26 fewer to 55 fewer). For patients treated between 3 to 6 hours, the OR for this outcome was 0.97 (95%CI 0.85 to 1.09). A meta-analysis of individual patient data from 6756 patients in nine randomized trials (RCTs) comparing alteplase with placebo or open control (9) found alteplase to be associated with increased odds of a good stroke outcome at three to six months (defined as a modified Rankin Score of 0 or 1) when administered within 4.5 hours of stroke onset, with earlier treatment (within 3 hours) associated with greater proportional benefit, irrespective of patient age or stroke severity.

Harms

The application presented a summary of the key safety outcomes reported in the 2014 Cochrane systematic review (8). Alteplase was associated with a greater proportion of patients experiencing early death (all causes, within seven to 10 days) compared to control (OR 1.44, 95%CI 1.18 to 1.76, p=0.0003; 5535 participants) corresponding to 25 more deaths per 1000 participants treated in absolute terms (95%CI 11 more to 40 more). Alteplase was associated with a significant increase in the rate of fatal intracranial haemorrhage (ICH) within seven to 10 days compared to control (OR 4.18, 95%CI 2.99 to 5.84, p<0.00001; 6683 participants) corresponding to 30 additional ICH per 1000 treated participants in absolute terms (95%CI 20 to 40). Early death due to causes other than fatal ICH occurred in 5.2% of alteplase treated patients compared with 5.7% of the control group (OR 0.93, 95%CI 0.73 to 1.18, p=0.54, 5303 participants). There was no significant effect observed on deaths from all causes during follow-up (three to six months) between alteplase and control (OR 1.06, 95%CI 0.94 to 1.20; 7012 participants), corresponding to 7 more deaths per 1000 participants treated (95%CI 2 fewer to 25 more). Orolingual angioedema associated with alteplase administration has been reported in case series studies (10, 11).

Cost / cost effectiveness

The application reports the price for a single IV dose of 63 mg alteplase for a 70 kg patient to range from US$ 260 (Brazil, public hospital) to US$ 6400 (average billing amount in the United States) (19, 20). Implementing and administering alteplase within the recommended 4.5 hours requires some initial investments in pre-hospital and intrahospital services. Many of these investments (such as stroke unit surveillance and care) will benefit stroke patients anyway, independently of thrombolysis being offered or not. These additional costs have to be balanced by generally shorter hospital stays, reduced rehabilitation needs, and reduced long-term care (including nursing homes and home care), given the reduction of handicap from thrombolysis (21). The UK National Institute for Health and Care Excellence (NICE) concluded the cost for all treatment windows up to 4.5 hours were below accepted willingness-to-pay thresholds for alteplase (19). In another United Kingdom-based model, the authors concluded that any strategy that increases thrombolysis rates will result in cost savings and improved patient quality of life (22). Studies from China and Brazil have also found alteplase treatment to be a cost-effective intervention (23, 24). A review of 16 studies of the cost-effectiveness of IV alteplase thrombolysis from Australia, Canada, China, Denmark, New Zealand, Spain, the United States and the United Kingdom, found that alteplase was a dominant or cost-effective strategy compared with traditional treatment in all but one of the studies (25).

WHO guidelines

WHO does not have approved guidelines for the management of AIS. “Treatment of acute ischaemic stroke with intravenous thrombolytic therapy” was included as a policy option and cost-effective intervention in the draft updated Appendix 3 of the Global Action Plan for the prevention and control of non-communicable diseases 2013–2020, to assist Member States in implementing actions to achieve targets for prevention and control of NCDs (12). Use of IV alteplase within 4.5 hours of stroke onset is recommended in multiple national and international guidelines (13–18).

Availability

Alteplase has marketing approval in 104 countries globally. The 10 mg and 20 mg strengths may not be available in all jurisdictions.

Other considerations

The Committee noted the use in practice of alteplase in acute myocardial infarction (MI) and considered that it is likely that alteplase would be used for this indication in some settings. The Committee noted that the EML currently includes streptokinase for MI and would welcome a future application reviewing the evidence for streptokinase and alteplase for this indication. Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the addition of alteplase to the EML, stating that it is a useful and effective drug and lowers morbidity and mortality associated with stroke when utilized correctly, and that cost-effectiveness had been demonstrated in various settings. The technical unit also noted that use of alteplase requires organized pre- and in-hospital care pathways in stroke-ready facilities, clinical training in diagnosing stroke, capacity to perform and interpret acute neuroimaging, continuous surveillance for at least 24 hours, and basic stroke management skills.

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