Alteplase

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

Codes ATC: B01AD02

Indication	Cerebral ischaemic stroke Code ICD11: 8B11
INN	Alteplase
Type de médicament	Chemical agent
Type de liste	Liste complémentaire
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
Historique des statuts LME	Ajouté pour la première fois en 2019 (TRS 1021)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Lire la suite sur les brevets.
Wikipédia	Alteplase
DrugBank	Alteplase

Recommandation du comité d'experts

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.

Contexte

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.

Pertinence pour la santé publique

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).

Bénéfices

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.

Torts

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).

Rapport coût/efficacité

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).

Directives de l'OMS

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).

Disponibilité

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

Autres considérations

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.

1. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016;15(9):913–24.
2. Global Burden of Disease compare data visualization. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2016. Available from https://vizhub.Healthdata.Org/gbd-compare/, accessed 29 September 2019.
3. Vanacker P, Lambrou D, Eskandari A, Mosimann PJ, Maghraoui A, Michel P. Eligibility and Predictors for Acute Revascularization Procedures in a Stroke Center. Stroke. 2016;47(7):1844–9.
4. Aguiar de Sousa D, von Martial R, Abilleira S, Gattringer T, Kobayashi A, Gallofré M et al. Access to and delivery of acute ischaemic stroke treatments: A survey of national scientific societies and stroke experts in 44 European countries. Eur Stroke J. 2019;4(1):13-28.
5. Schwamm LH, Ali SF, Reeves MJ, Smith EE, Saver JL, Messe S et al. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at Get With The Guidelines-Stroke hospitals. Circ Cardiovasc Qual Outcomes. 2013;6(5):543–9.
6. Urimubenshi G, Cadilhac DA, Kagwiza JN, Wu O, Langhorne P. Stroke care in Africa: A systematic review of the literature. Int J Stroke. 2018;13(8):797–805.
7. Pandian JD, William AG, Kate MP, Norrving B, Mensah GA, Davis S et al. Strategies to Improve Stroke Care Services in Low- and Middle-Income Countries: A Systematic Review. Neuroepidemiology. 2017;49(1-2):4561.
8. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014(7):CD000213.
9. 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(9958):1929–35.
10. Engelter ST, Fluri F, Buitrago-Tellez C, Marsch S, Steck AJ, Ruegg S et al. Life-threatening orolingual angioedema

during thrombolysis in acute ischemic stroke. J Neurol. 2005;252(10):1167–70.
11. Hill MD, Lye T, Moss H, Barber PA, Demchuk AM, Newcommon NJ et al. Hemi-orolingual angioedema and ACE in hibition after alteplase treatment of stroke. Neurology. 2003;60(9):1525–7.
12. Preparation for the third High-level Meeting of the General Assembly on the Prevention and Control of Non-com municable Diseases, to be held in 2018 - Report by the Director-General. Geneva: World Health Organization; 2018. Available from http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_27-en.pdf, 29 September 2019.
13. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American H eart Association/American Stroke Association. Stroke. 2018;49(3):e46–e110.
14. Boulanger JM, Lindsay MP, Gubitz G, Smith EE, Stotts G, Foley N et al. Canadian Stroke Best Practice Recommen dations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th E dition, Update 2018. Int J Stroke. 2018;13(9):949–84.
15. Bryer A, Connor M, Haug P, Cheyip B, Staub H, Tipping B et al. South African guideline for management of ischa emic stroke and transient ischaemic attack 2010: a guideline from the South African Stroke Society (SASS) and the SASS Writing Committee. S Afr Med J. 2010;100(11 Pt 2):747–78.
16. Dong Q, Dong Y, Liu L, Xu A, Zhang Y, Zheng H et al. The Chinese Stroke Association scientific statement: intrav enous thrombolysis in acute ischaemic stroke. Stroke Vasc Neurol. 2017;2(3):147–59.
17. Michel P, Engelter S, Arnold M, Hungerbühler HJ, Nedeltchev K, Georgiadis D et al. Thrombolyse de l'attaque cér ébrale ischémique : Recommandations actualisées. Swiss Medical Forum. 2009;9(49):982–4.
18. Cho KH, Ko SB, Kim DH, Park HK, Cho AH, Hong KS et al. Focused Update of Korean Clinical Practice Guidelines f or the Thrombolysis in Acute Stroke Management. Korean J Stroke. 2012;14:95–105.
19. Holmes M, Davis S, Simpson E. Alteplase for the treatment of acute ischaemic stroke: a NICE single technology a ppraisal; an evidence review group perspective. Pharmacoeconomics. 2015;33(3):225–33.
20. Kleindorfer D, Broderick J, Demaerschalk B, Saver J. Cost of Alteplase Has More Than Doubled Over the Past Dec ade. Stroke. 2017;48(7):2000–2.
21. Dirks M, Baeten SA, Dippel DW, van Exel NJ, van Wijngaarden JD, Huijsman R et al. Real-life costs and effects of an implementation program to increase thrombolysis in stroke. Neurology. 2012;79(6):508–14.
22. Penaloza-Ramos MC, Sheppard JP, Jowett S, Barton P, Mant J, Quinn T et al. Cost-effectiveness of optimizing acut e stroke care services for thrombolysis. Stroke. 2014;45(2):553–62.
23. Pan Y, Chen Q, Zhao X, Liao X, Wang C, Du W et al. Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke in China. PLoS One. 2014;9(10):e110525.
24. Araujo DV, Teich V, Passos RB, Martins SC. Analysis of the cost-effectiveness of thrombolysis with alteplase in st roke. Arq Bras Cardiol. 2010;95(1):12–20.
25. Joo H, Wang G, George MG. A literature review of cost-effectiveness of intravenous recombinant tissue plasmino gen activator for treating acute ischemic stroke. Stroke Vasc Neurol. 2017;2(2):73–83.

