Tenecteplase (and common sense) in short supply during the COVID-19 pandemic

Recent proposals to adopt tenecteplase as the recommended thrombolytic agent for stroke reperfusion will reduce its availability for patients with acute myocardial infarction

The coronavirus disease 2019 (COVID-19) pandemic has had a huge impact on medical practice, with pharmaceutical supply chains compromised across the world.[1] Tough decisions with respect to rationing of resources in acute health care have necessarily been made. However, we are concerned about health policy decisions in stroke thrombolysis being made without the requisite level of evidence and, even more troublingly, with lack of consideration for the flow-on effects on thrombolytic drug supply for patients with myocardial infarction (MI). On 17 April 2020, Boehringer Ingelheim Australia (manufacturer of a tenecteplase product) noted the unprecedented demand for tenecteplase in Australia, possibly "due to the desire to increase safety stock holding; possible changes in clinical management of [ST elevation myocardial infarction] patients, with potential closure of [percutaneous coronary intervention] facilities leading to increased demand for thrombolysis; and … potential for off-label use of tenecteplase in patients with acute ischaemic stroke" (Marika Tetere, Medical Director Australia and New Zealand, Boehringer Ingelheim, personal communication). The company indicates that there is a limited supply of tenecteplase, and "due to a complex production process and capacity limitations driven by global demand, it is not possible to scale-up production to supply tenecteplase at the high levels the above mentioned changes require" (personal communication, as above). This is because tenecteplase is recombinant technology produced by cell culture with a limited production. If this increased demand for tenecteplase outstrips its fixed supply, it will almost certainly lead to a period of tenecteplase being unavailable in Australia. Concerningly, recent proposals (that have accelerated during the COVID-19 crisis) to adopt tenecteplase as the recommended thrombolytic agent for stroke reperfusion will potentially limit access to tenecteplase for patients with acute MI. This is of particular concern in rural Australia where tenecteplase is the current emergency treatment for acute MI (often pre-hospital) in order to offer timely myocardial revascularisation. This lifesaving treatment is at risk if the stroke community moves to tenecteplase at this stage. Importantly, tenecteplase has level 1 evidence as a thrombolytic for MI, but not yet for acute stroke, where the closely related agent alteplase is the only licensed stroke thrombolytic in Australia, North America, Asia and Europe.

Tenecteplase is yet to be proven non-inferior (let alone superior) to alteplase, the current standard of care in acute stroke. There have been two (Australian-led) phase 2 studies showing the superiority of tenecteplase over alteplase for patients with large vessel occlusion (LVO) stroke using surrogate brain imaging outcomes (early reperfusion or recanalisation).[2,3] These findings (and other international trial data) have driven a recent meta-analysis suggesting that tenecteplase may be non-inferior to alteplase.[4] The meta-analysis has generated international enthusiasm to switch from alteplase to tenecteplase for all acute stroke patients eligible for thrombolysis, but the enthusiasm has been particularly marked in Australia and New Zealand. It is worth bearing in mind that LVO stroke, while the most severe stroke syndrome, only comprises 15–20% of thrombolysis-eligible stroke. Further, a meta-analysis of phase 2 trials not supported by at least one positive phase 3 pivotal study should not be enough to change clinical practice. Indeed, there are no phase 3 data showing non-inferiority (or superiority) of tenecteplase compared with alteplase for thrombolysis-eligible stroke. The American Stroke Association guidelines comment that it "may be reasonable" in LVO to use tenecteplase as a substitute for alteplase in patients moving to endovascular therapy, but classify the level of this recommendation as weak and based on only moderate quality evidence.[5] The guidelines are even more cautious in the non-LVO population, noting that tenecteplase "has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment".[5] The European Stroke Organisation provides no recommendation for use of tenecteplase outside of LVO stroke, and the LVO recommendation is weak (expert opinion).[6] The recently updated Australian guidelines recommend that tenecteplase or alteplase could be used for LVO, and also have a weak recommendation that tenecteplase could be used as an alternative in other stroke patients.[7] This is not a recommendation of superiority of tenecteplase over alteplase and, especially in the current context of constrained tenecteplase supply, should not be interpreted as recommending a shift in practice towards tenecteplase. Previous medico-legal issues with stroke thrombolysis, where the majority of litigation has occurred due to patients not being administered alteplase, should also be considered. Would, for example, a patient suffering a serious bleeding complication with tenecteplase make ligation more likely to be successful given the patient did not receive standard of care alteplase?[8] Indeed, some emergency physicians have been reluctant to accept the national guidelines for stroke thrombolysis treatment.[9] Thus, it would seem a retrograde step to now recommend a treatment (tenecteplase) that currently does not have approval for stroke.

In an attempt to generate the requisite level of evidence to appropriately translate the use of tenecteplase for stroke thrombolysis into clinical

Mark Parsons[1,2]
Leonid Churilov[3]
Aletta E Schutte[4]
Christopher Levi[5]

1 Melbourne Brain Centre, Royal Melbourne Hospital, Melbourne, VIC.
2 South Western Sydney Clinical School, UNSW, Sydney, NSW.
3 University of Melbourne, Melbourne, VIC.
4 UNSW, Sydney, NSW.
5 Sydney Partnership for Health, Education, Research and Enterprise, Sydney, NSW.

markp@unimelb.edu.au

doi: 10.5694/mja2.50836

practice, an ongoing international phase 3 trial of tenecteplase versus alteplase for stroke thrombolysis-eligible patients is currently underway (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12613000243718). Another similar trial, again enrolling all potentially thrombolysis-eligible stroke patients, is being conducted in the United Kingdom (https://clinicaltrials.gov/ct2/show/NCT02814409). We stress the importance of successful recruitment to the current tenecteplase trials to obtain more precise estimates of the difference (if any) between these two thrombolytics in acute stroke. Of course, the recent guideline changes (made just before the COVID-19 pandemic) could have potential impact on clinical trial recruitment. However, with the onset of the pandemic (which has already led to major challenges for clinical trials), several Australian and New Zealand stroke expert committees, along with Australian jurisdictional telestroke networks, have recommended (or have already made the change to) tenecteplase as the sole thrombolytic for stroke. This includes Victoria and Tasmania, South Australia, Queensland, and both North and South Island telestroke networks in New Zealand. A notable exception is the NSW Stroke Network, which unanimously supported continuing the use of alteplase within that state, particularly as it is currently rolling out a new statewide telestroke service. The rationale for switching to promotion of tenecteplase is that its ease of administration (single bolus versus one hour infusion) would reduce some burden on inter-hospital transfers. On the contrary, however, there is a risk of serious dosing errors in switching to tenecteplase, given the different doses and different intravenous administration protocols (single bolus with tenecteplase versus bolus plus infusion with alteplase).

We are aware of some off-label use of tenecteplase for stroke in other countries (eg, France), but the move towards such use in Australia and New Zealand is out of step with the rest of the international community. In the context of a potential shortage, coupled with the absence of high level evidence, convenience should not become a compelling reason to switch to tenecteplase for stroke. The use of tenecteplase as the sole thrombolytic for stroke is not supported by the available evidence and fails to consider the substantial opportunity cost of patients with acute MI not being able to access standard of care treatment with tenecteplase.

In cardiac reperfusion, a pressing concern during the COVID-19 pandemic is the risk of virus transmission during cardiac catheterisation for ST-elevation MI (STEMI).[10] Bringing a COVID-19-positive patient (recognised or unrecognised) to the laboratory exposes staff to risk of infection and prevents further laboratory use until sterilisation is performed. Undoubtedly, there will be delays in patients accessing primary percutaneous coronary intervention (PPCI), meaning that the outcome benefits of PPCI, as opposed to giving intravenous tenecteplase, may be lost. As a result, some centres in China (and also in Italy and Spain) have suspended PPCI services and proposed intravenous thrombolysis for all STEMI during the pandemic, although other countries, including Australia and the US, have recommended either treatment as an option.[10,11] Most of the cardiology community would not be aware of the push to use tenecteplase for stroke thrombolysis, and hence would not be cognisant that moving to tenecteplase rather than PPCI (where it is available) for STEMI would further deplete current supply, potentially leading to even longer periods of supply interruption. Further, in Australia and other large countries, where rapid PPCI access is limited by geographical constraints, pre-hospital and small hospital lysis programs currently exist for STEMI. These protocols solely use tenecteplase, meaning an interruption in supply would further disadvantage regional and rural patients, a population already suffering poorer cardiovascular outcomes.

It is notable that acute MI is the only licensed indication for tenecteplase in virtually all countries worldwide. We maintain that there is no compelling reason to switch to tenecteplase for stroke, particularly when we are facing a supply shortage. Difficult times typically call for rational decisions, and not for premature translation. This is yet another example of unintended consequences, despite the best of intentions, occurring during the COVID-19 pandemic.

Competing interests: Mark Parsons is a member of a global advisory board on tenecteplase for Boehringer Ingelheim.

Provenance: Not commissioned; externally peer reviewed. ■

The unedited version of this article was published as a preprint on mja.com.au on 30 July 2020.

References are available online.

1 Tucker E, Daskin M. Medical supply chains are fragile in the best of times and COVID-19 will test their strength. *The Conversation* 2020; 25 Mar. https://theconversation.com/medical-supply-chains-are-fragile-in-the-best-of-times-and-covid-19-will-test-their-strength-133688 (viewed Sept 2020).

2 Parsons MW, Spratt N, Bivard A, et al. A Randomized trial of tenecteplase versus alteplase for acute ischemic stroke *N Engl J Med* 2012; 366: 1099–1107.

3 Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018; 378: 1573–82.

4 Burgos AM, Saver JL. Evidence that tenecteplase is non-inferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials. *Stroke* 2019; 50: 2156–2152.

5 Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke. *Stroke* 2019; 50: e344–e418.

6 Turq G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy for acute ischemic stroke. *J Neurointerv Surg* 2019; 11: 535–538.

7 Stroke Foundation. Clinical Guidelines for Stroke Management. Melbourne: Stroke Foundation, 2019. https://informme.org.au/Guidelines/Clinical-Guidelines-for-Stroke-Management (viewed Sept 2020).

8 Bhatt A, Safdar A, Chaudari D, et al. Medicolegal considerations with intravenous tissue plasminogen activator in stroke: a systematic review. *Stroke Res Treat* 2013; 2013: 562564.

9 Smith BJ. Thrombolysis for acute stroke in Australia. *Med J Aust* 2011; 194: 212. https://www.mja.com.au/journal/2011/194/4/thrombolysis-acute-stroke-australia.

10 Zaman S, MacIsaac AI, Jennings GLR, et al. Cardiovascular disease and COVID-19: Australian/New Zealand consensus statement. *Med J Aust.* 2020; 213(4): 182–187. https://www.mja.com.au/journal/2020/213/4/cardiovascular-disease-and-covid-19-australian-and-new-zealand-consensus.

11 Zeng J, Huang J, Pan L. How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People's Hospital. *Intensive Care Med* 2020; 46: 1111–1113. ■