The Medical Journal of Australia – Pre-print – 30 July 2020

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

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Disclosure statement:
Professor Parsons is a member of a global advisory board for Tenecteplase for Boehringer Ingelheim

Professor Parsons, Professor Levi, and Professor Churilov are on the steering committee of the TASTE trial which is investigating tenecteplase versus alteplase for stroke thrombolysis

Brief Abstract

The Covid-19 pandemic has compromised pharmaceutical supply chains across the world. During the pandemic, there has been unprecedented demand for Tenecteplase in Australia. This could lead to a period of Tenecteplase being unavailable in Australia. Concerningly, recent proposals (accelerated during the Covid-19 crisis) to adopt Tenecteplase as the recommended thrombolytic agent for stroke reperfusion will put at risk access of acute myocardial infarction (MI) patients to Tenecteplase, particularly in rural Australia. Tenecteplase has level I evidence as a thrombolytic for MI, but not yet for acute stroke, where the closely related agent Alteplase is the only licensed stroke thrombolytic.

The 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 healthcare 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 myocardial infarction patients. Correspondence released on April 17 from Boehringer Ingelheim (BI) Australia states that "the company has seen unprecedented demand for Metalyse (tenecteplase) in Australia. This may be due to the desire to increase safety stock holding; possible changes in clinical management of STEMI (ST Elevation Myocardial Infarction) patients, with potential closure of PCI facilities leading to increased demand for thrombolysis; and possible/potential for off-label use of tenecteplase in patients with acute ischaemic stroke".[2] 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." 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 this 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 put at risk access of acute myocardial infarction (MI) patients to Tenecteplase. 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 move to Tenecteplase at this stage. Importantly, Tenecteplase has level I 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 the current standard of care Alteplase in acute stroke. There have been two (Australian-led) phase II studies showing superiority of Tenecteplase compared to Alteplase for patients with large vessel occlusion (LVO) stroke using surrogate brain imaging outcomes (early reperfusion/recanalisation).[3,4] This (and other international trial data) has driven a recent meta-analysis suggesting that Tenecteplase may be non-inferior to Alteplase.[5] This 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, whilst the most severe stroke syndrome, only comprises 15-20% of thrombolysis eligible stroke. Further, a meta-analysis of Phase II trials not supported by at least one positive Phase III pivotal study should not be enough to change clinical practice. Indeed, there is no phase III data showing non-inferiority (or superiority) of Tenecteplase compared to Alteplase for thrombolysis-eligible stroke. The American Stroke Association (ASA) guidelines comment that it "may be reasonable" in LVO to use Tenecteplase as a substitute for Alteplase in patients moving to receive endovascular therapy, but classify the level of this recommendation as "weak" and based on only "moderate quality" evidence.[6] ASA guidelines are even more cautious in the non-LVO population noting Tenecteplase "has not been proven to be superior or non-inferior to alteplase, but might be considered as an alternative to alteplase in patients with minor neurological impairment"**.** The European Stroke Organisation provides no recommendation for use of Tenecteplase outside of LVO stroke, and, the LVO recommendation is weak (expert opinion).[7] The recently updated Australian guidelines recommend that Tenecteplase or Alteplase could be used for large vessel

occlusion, and also have a weak recommendation that Tenecteplase could be used as an alternative in other stroke patients.[8] 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. Another issue to consider are the medico-legal difficulties in the past with stroke thrombolysis. 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 into clinical practice the use of Tenecteplase for stroke thrombolysis, there is an ongoing international phase III trial of Tenecteplase versus Alteplase for Stroke Thrombolysis Eligible patients (TASTE). Another similar trial, again enrolling all potentially thrombolysis-eligible strokes, is being conducted in the United Kingdom (Alteplase-Tenecteplase Trial Evaluation for Stroke Evaluation Thrombolysis, ATTEST-2).[10] 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 prior to the Covid-19 pandemic) could have potential impact on clinical trial recruitment. However, with the onset of the Covid-19 pandemic (which already has led to major challenges for clinical trials) several Australian state and New Zealand Stroke expert committees, and Australian state telestroke networks, have recommended (or, have already made the change) to use Tenecteplase as the sole thrombolytic for stroke. This includes Victoria/Tasmania, South Australia, Queensland, and both North and South Island telestroke networks in New Zealand.[11] A notable exception is the NSW Stroke Network, which unanimously supported continuing using alteplase within that State, particularly as this State is currently rolling out a new funded

statewide telestroke service. The rationale for switching to Tenecteplase being promoted is that its ease of administration (single bolus versus one hour infusion) would reduce some burden on inter-hospital transfers. On the contrary, given the known difficulty in clinician behaviour change, there is a risk of serious dosing errors in switching to Tenecteplase given the different doses and different IV administration protocols (single bolus with Tenecteplase versus bolus plus infusion with Alteplase).

We are aware of similar off-label use of Tenecteplase for stroke in other countries, but the move towards off-label use of Tenecteplase for stroke 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 definitely irrational when one considers the combination of available evidence, together with the substantial opportunity cost of acute MI patients 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).[11] 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 (also in Italy and Spain) have suspended PPCI services and proposed intravenous thrombolysis for all STEMI during the

pandemic, although other countries have recommended either treatment as an option. This includes Australia and the US.[12,13] 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 the current supply of Tenecteplase, potentially leading to even longer periods of supply interruption. Furthermore, 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/rural patients, a population already suffering poorer cardiovascular outcomes.

It is notable that the only licensed indication for Tenecteplase, in virtually all countries worldwide, is acute MI. 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.

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