The cost of teriflunomide in the treatment of relapsing-remitting multiple sclerosis

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ABSTRACT

AIMS: Teriflunomide, used globally to treat multiple sclerosis (MS) and widely subsidised for this indication including in Australia and New Zealand, is the main metabolite of leflunomide, an older immune-modulating drug. Leflunomide therefore represents a potential alternative therapy for MS. Teriflunomide is about 50–500 times more expensive than leflunomide, depending on prices in each jurisdiction. I wished to study how this situation arose.

METHODS: Web search to obtain the publicly available minutes of eight international regulatory bodies that have approved teriflunomide for the governments of the US, Canada, Europe, England, Scotland, Australia (TGA and PBS) and New Zealand, and examination of the processes and minuted discussions concerning the metabolic, efficacy, toxicity and cost relationship between teriflunomide and leflunomide.

RESULTS: The relationship between the two drugs and their relative efficacy or toxicity in MS was considered by three of eight agencies (Food and Drug Administration (FDA), European Medicines Agency (EMA) and the Canadian Agency for Drugs and Technology in Health (CADTH)). The remaining agencies accepted teriflunomide applications at face value, assessed cost-effectiveness against contemporaneous drugs used for treating MS, and did not discuss the potential role of leflunomide as a therapy for MS. No agency minuted the implications of the cost difference.

CONCLUSIONS: Efficacy for leflunomide in MS is likely but unproven. The sponsor presented a case for teriflunomide that was within the established procedures for drug agencies in establishing cost-effectiveness, and agencies did not stray from their normal procedures. As a result, an opportunity to decrease the cost of treating MS has been missed. Though off-label use of leflunomide is possible, this is unlikely without a publicly-funded trial to demonstrate non-inferiority with regard to efficacy and safety.
Teriflunomide was granted subsidy in both New Zealand and Australia following assessment by the respective advisory committees: the Pharmacology and Therapeutics Advisory Committee (PTAC) (which advises PHARMAC and in turn the New Zealand Government)\(^1\) and the Pharmaceutical Benefits Advisory Committee (PBAC),\(^2\) which advises the Australian Government via the Department of Health. As licensing and subsidy approvals are separate processes in Australia, the drug was also examined by the Therapeutic Goods Administration (TGA).\(^3\) Teriflunomide was also registered in the US (Food and Drugs Administration, FDA)\(^4\) and subsidised across Europe following the advice of the European Medicines Agency (EMA),\(^5\) and in England (National Institute of Health and Care Excellence, NICE),\(^6\) Scotland (Scottish Medicines Consortium, SMC)\(^7\) and Canada (Canadian Agency for Drugs and Technologies in Health, CADTH).\(^8\) Subsidised availability in these jurisdictions is for the treatment of relapsing-remitting multiple sclerosis, with minor variations among jurisdictions such as restriction, or not, to single drug use.

Teriflunomide is the active metabolite of leflunomide, an older immunosuppressant drug also developed by Sanofi-Aventis. Leflunomide was registered in 1998 for use as a biological DMARD (disease modifying anti-rheumatic drug) in rheumatoid and psoriatic arthritis. Seventy percent of leflunomide is metabolised to teriflunomide.\(^4,9\) Leflunomide has four minor metabolites whose biological activity is uncertain. Thus leflunomide is a pro-drug for teriflunomide, and teriflunomide is the active metabolite. The unit tablet sizes are 20 and 14mg daily respectively. A patient taking a daily dose of 20mg of leflunomide generates, by metabolism at the above rate, the same quantity of teriflunomide per day that is in one tablet of that drug.\(^4\) It therefore appears logical that, other things being equal, a benefit of teriflunomide 14mg daily in any registered indication for either would be obtained if the patient was instead given leflunomide 20mg. However, leflunomide has not been tested in multiple sclerosis, nor has teriflunomide been trialled in rheumatoid or psoriatic arthritis.

In all jurisdictions, there is a substantial cost difference between the two drugs. For example, in New Zealand the cost of leflunomide is NZ$2.90 for 30 tablets (9.7 c/tab!) versus NZ$1,582.62 for 28 tablets of teriflunomide (NZ$56.52/tab),\(^10\) a price ratio per tablet of 584. Corresponding figures in Australia are AU$1.47 and $65.62 per tablet, a ratio of 44.6.\(^11\) The low New Zealand price for leflunomide presumably reflects the PHARMAC drug tendering process as applied to generic drugs. A respectable logical but unproven case can be made that teriflunomide, which has been determined in each of the above jurisdictions to be cost-effective compared to current treatments for multiple sclerosis, would be dominated by leflunomide in an economic model that used it as a comparator and assumed therapeutic and safety equivalence. Or to put it another way, it could be argued that having demonstrated cost-effectiveness of teriflunomide, prescribing leflunomide to patients with multiple sclerosis would be reasonable because of its pro-drug status, would probably obtain identical clinical benefits, be more cost-effective and avoid substantial costs.

It is legitimate to ask why this logic was not used by any of the international drug regulatory bodies that considered the registration and subsidy of teriflunomide.

**Methods**

This discussion is based on internet searches entitled ‘teriflunomide minutes in [name of jurisdiction]’ or specific searches with the search term ‘teriflunomide’ within websites for specific regulatory bodies such as the TGA, PBAC and PTAC. Countries such as Switzerland where the relevant documents are not in English were excluded. The minutes obtained were scrutinised to determine the extent to which a connection between leflunomide and teriflunomide was acknowledged and further discussed, and the nature of these discussions. Some available minutes are of a summary nature and the full minutes are confidential. For example, in Australia only a Public Summary Document of PBAC decisions is published.

Subsidy data for PBS (Australian) use of teriflunomide for the 2017–2018 financial year were obtained from Australian Government Department of Human Services website.\(^12\)
Results with comment

The results are summarised in Table 1. All agency minutes acknowledged, usually in a single sentence, that teriflunomide is the predominant metabolite of leflunomide. Only the FDA and EMA minutes\(^5,6\) state that the 20mg tablet of leflunomide will generate the unit dose (14mg) of teriflunomide, and only these two agencies explicitly discuss the implications for this relationship for either efficacy or safety (particularly the latter). One FDA delegate was critical of the sponsor for allegedly seeking to minimise or obscure the toxicity of teriflunomide given the known toxicity of leflunomide, especially hepatotoxicity and toxicity related to pregnancy.\(^12\)

These were aspects that in the past nearly led to the withdrawal of leflunomide. Suggested brief organ-specific toxicity proposed by the sponsor for the US teriflunomide Drug Product Information sheet were rejected in most cases by the FDA in favour of the descriptions already listed for leflunomide.\(^12\)

Thus in effect, the FDA suggested that the two drugs must have the same toxicity. However, the FDA did not discuss any effect of drug similarity on whether teriflunomide should be given marketing approval. CADTH provided a summary of leflunomide toxicity for each organ system before discussing the corresponding trial evidence for teriflunomide, strongly implying by that device that similarity of toxicity was anticipated.\(^8\) In the case of EMA, the discussion arose around the question of whether teriflunomide should be allocated ‘new drug’ status, as discussed below.

The remaining agencies adopted a traditional approach in which the comparator drug or drugs (mainly interferon β\(^1\)a, interferon β\(^1\)b or glatiramer) were apparently accepted at face value and the economic models were scrutinised in the usual way, taking into account the trials against placebo and active drug that had been organized by the sponsor. Each agency concluded that teriflunomide had modest efficacy advantages over these drugs, and its ability to be administered by mouth was given due weight. Thus it was accepted as being economically dominant over contemporaneous treatments, and subsidised accordingly. The relative clinical and economic performance over fingolimod (also given orally) was not tested.

Extracts from agency reports

According to the EMA report,\(^5\) “Teriflunomide is the active main metabolite of leflunomide. The non-clinical development of teriflunomide was originally guided by experience gained with the parent compound leflunomide in terms of study designs and anticipated target organ toxicities. Nevertheless, an independent self-standing development of teriflunomide was later pursued non-clinically [refers to pre-clinical development: Auth], because of the intended use of teriflunomide as treatment in multiple sclerosis as opposed to the different indication.”

### Table 1: Drug regulatory agency minute contents relating to comparisons between leflunomide and teriflunomide. The ‘IMPLIED’ entry for CADTH discussions of safety matters is explained in the text.

<table>
<thead>
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<th>Drug agency</th>
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<th>Discussion of safety equivalence</th>
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*In discussion over whether teriflunomide should be assigned ‘new drug’ status. For agency acronyms, see text.
of leflunomide (Report, p 14)…Teriflunomide exposure after a single 20mg dose of leflunomide was ~70% of that after a single 20mg dose of teriflunomide. Leflunomide was shown to be effective in patients with rheumatoid arthritis at doses of 10 and 20mg. In Phase 2 of development of leflunomide, higher incidences of adverse events were observed with the dose of 25mg and consequently, the decision was made to test the doses of 10mg and 20mg of leflunomide in Phase 3 studies. These results were also taken into account for the development of teriflunomide and the decision was made not to test doses of teriflunomide higher than 14mg. The applicant made a presumption of a 1:1 transmission of effective doses developed in RA to MS referring to the hypothesis that in both indications, the effect of teriflunomide on the DHO-DH enzyme would result in a clinical effect” (Report, p 33). These entries suggest that the EMA accepted that the actions of leflunomide and teriflunomide would be identical.

The EMA also assessed whether teriflunomide is a ‘new drug’ because of its policy that “The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy”. Whether teriflunomide is a new drug thus relied on the interpretation of “derivatives”. The complex argument on this point makes interesting reading. One difference cited by the sponsor was the potential for greater hepatotoxicity with leflunomide because its metabolism generates 4 minor metabolites not present after teriflunomide. However, the agency felt that “…the potentially lower hepatotoxic potential of teriflunomide is of minor clinical relevance with no significant benefits for patients treated with teriflunomide”. The conclusion was that though teriflunomide satisfied other criteria for marketing, it was not a new active drug, and further, that the effects of leflunomide were wholly mediated via teriflunomide. The sponsor appealed this decision using even more complex arguments and succeeded in overturning it on the basis of possible toxicity differences. A dissenting opinion to the effect that the evidence of such a difference was unacceptably weak was signed by nine members of the Committee and published as an Appendix to the EMA report.

The FDA documents state12 that “The advantage of teriflunomide versus leflunomide as an investigational drug for the treatment of multiple sclerosis (MS) is based largely on the ability to administer the active drug directly. Direct ingestion of only the active metabolite negates the need for formation of the active metabolite and ensures a more consistent delivery and higher bioavailability independent of enzymic conversion which may be impaired in the presence of concomitant drugs or under certain disease conditions.” These are hardly substantial advantages. The FDA report also voiced strong criticisms related to toxicity. The FDA required rewriting of detailed toxicity by organ to ensure that the descriptions matched the corresponding entries for leflunomide. One contributor was scathing over a six-year delay in notification of a case of toxicity, and in describing alleged behaviour of the sponsor in minimising teriflunomide toxicity. The delegate stated “It is understandable that the sponsor might like to extend the useful life of an old drug leflunomide, now off patent, by seeking new patients and new uses for teriflunomide, but not by concealing adverse events to physicians who may not be fully aware of them”. It is not clear whether the charge of “concealing” has any evidential basis.

Discussion

The usual comparator drug accepted in pharmacoeconomic analysis is the drug most likely to be replaced in clinical practice. In Australia, this may be the PBS-listed drug for the same indication, but unlisted drugs or even “existing pharmacological analogues” may serve as comparators.13 This makes sense because the economic effect of a new drug can only be judged according to a comparison with current treatment and how it will be improved by substitution of its effects on disease outcomes and toxic reactions by the new agent. There is no provision in any jurisdiction for considering a metabolic precursor as a comparator drug and indeed this does not make sense, and is not possible according to current procedures, if the parent drug is not registered and therefore not used in the proposed indication.

The questions arising from this work are whether the benefit of teriflunomide might be achieved at a fraction of the cost by using leflunomide, whether a predominant metabolite of a pro-drug should be given new drug status, and why these questions and the matter of relative cost were apparently
not considered by any of eight international drug regulatory agencies.

With the possible qualification related to the comments in FDA minutes over minimisation of potential toxicity of teriflumonide, the sponsor of teriflumonide made legal use of the systems created internationally for marketing and subsidy of new drugs, as it was entitled to do. It is likely that Sanofi-Aventis/Genzyme recognised the possibility of marketing as a new drug the principal metabolite of the out-of-patent drug leflumonide, in a high-cost indication which was not a registered indication for the parent drug. If the ‘new’ drug was shown in trials to be effective when tested against existing costly therapies for MS, the sponsor could seek a high price while satisfying the usual criteria of cost-effectiveness. In spite of reservations regarding new drug status and criticisms over relative toxicity, it appears that under prevailing regulatory systems, success for the sponsor was likely from the outset, as the applications satisfied the defined scientific and economic criteria for granting subsidy that exist similarly worldwide. Nevertheless, it was a high-risk strategy, as no prior human evidence of possible efficacy for teriflumonide existed (studies in animal models had suggested a benefit). The company also faced the tangible risk that one or more of the regulatory agencies it had to deal with would not recognise teriflumonide as a new drug or would ask why it should not be administered as leflumonide, leading to application failure. In the event, most agencies (and the governments they report to) treated the teriflumonide application in a routine manner, and probing questions about the relationship with leflumonide were not asked or, if discussed, not minuted. Though absence of a formal minute does not necessarily mean that an issue was not discussed, in this case it is possible that discussions ensued but remained unminuted because no decision in respect of leflumonide was possible in the absence of supporting trial data. This possibility and this reason would not, however, have prevented any committee from minuting the detail of the metabolic relationship between the drugs, their common mechanism of action, the dosing equivalence and the substantial cost differences, to allow consideration by higher government authority.

These events happened in circumstances where there was no prima facie reason to assume that the two drugs differ in either their mode of action or clinical effects, and hence no scientific rationale to suggest that teriflumonide might be more effective than leflumonide in MS, and scant evidence of a difference in toxicity. The opportunity for a drastic reduction in the cost of treating multiple sclerosis by seeking a registration for leflumonide and testing that drug in patients with MS was not in the sponsor’s commercial interest. The agencies may have discussed but were unable to apply the presumptive argument that leflumonide and teriflumonide were likely to be equivalent, because of absence of trial data to confirm it. They were obliged to deal with the applications before them using predetermined procedures in good faith, and did so. On the positive side, it can be said that the global success of the teriflumonide applications expanded the therapeutic options available to neurologists in the treatment of MS and did not lead to a significant increase in the cost of treating MS compared to other treatments.

Conclusion

Governments in states that have subsidised teriflumonide pay about 50–500 times the cost (depending on the local prices including secretly negotiated prices for teriflumonide) arising if the patients were given leflumonide 20mg daily. This would generate by metabolism the same dose of teriflumonide that is now used in clinical practice. In Australia, the cost to government for teriflumonide amounted to AU$29.7m in the year to 30 June 2018. The estimated corresponding cost of leflumonide is about $666,000, subject to variation in the mix of patient category under the scheme, implying a possible saving of around $29m. Thus a potential opportunity to decrease substantially the cost of treating MS may have been missed. The only routes to obtain the cheaper option now lie in (a) executive action by a drug regulatory body or government to register leflumonide in MS; (b) off-label use of leflumonide by neurologists; or (c) by the design and execution of a randomised comparative trial of leflumonide versus teriflumonide in MS, funded by a non-commercial organisation such as NIH, MRC or NH&MRC. Given that equivalence has not been demonstrated and possible differences in toxicity, the first two options are not attractive, and only the third option appears practicable.
Competing interests:
Nil.

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