Saving money on the PBS: ranibizumab or bevacizumab for neovascular macular degeneration?

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The cost differential between these two drugs is no longer defensible

Federal Health Minister Nicola Roxon recently met with an alliance of consumer, industry and other stakeholders to justify the government's plan to indefinitely delay the listing of seven new medicines on the Pharmaceutical Benefits Scheme (PBS). She argued that, after considering the advice of the Pharmaceutical Benefits Advisory Committee (PBAC), it was the government's responsibility to decide whether or not to list a new drug, taking into account other priorities across the health portfolio and current fiscal circumstances.[1]

Clearly, the cost of the PBS must be sustainable. However, there are other ways of reducing its cost apart from delaying the listing of drugs recommended by PBAC as cost-effective. The treatment of macular degeneration provides an illustrative example.

Age-related macular degeneration (AMD) is responsible for almost half of all cases of blindness in Australia.[2] In neovascular (or "wet") macular degeneration, vision loss results from the abnormal growth and leakage of blood vessels in the macula. Ranibizumab (Lucentis), developed by Genentech and marketed by Novartis in Australia, is currently the only drug approved by the Therapeutic Goods Administration (TGA) and available on the PBS to treat wet AMD. It is administered as an intravitreal injection, usually 4–8-weekly, for 12 to 18 months or longer. The PBS-listed price of each injection is $1967. Ranibizumab is the antigen-binding fragment of a recombinant, humanised, monoclonal antibody that binds to vascular endothelial growth factor A (VEGF-A), the cytokine primarily responsible for blood vessel growth. The inhibition of VEGF-A reduces the permeability and growth of the neovascular vessels. Blindness is prevented in most patients, and the majority of treated patients go on to have some improvement in vision.[3-5]

Bevacizumab (Avastin) is an anti-VEGF-A humanised, monoclonal antibody (also developed by Genentech, and marketed in Australia by Roche; Genentech is a wholly owned subsidiary of Roche) that has been approved by the TGA for the systemic treatment of certain cancers. It was successfully used "off-label" for the treatment of wet AMD before ranibizumab became available, but has also been used to some degree since the availability of ranibizumab, especially in the United States, where patients bear more of the costs of drugs.[5-7] It is prepared for ophthalmic use in a sterile pharmacy by taking a dose used in chemotherapy and splitting it for use in treating wet AMD for up to 25 patients. The cost of its off-label use has been significantly less than that of ranibizumab (around a 40th of the cost, at $50 per dose).

Ranibizumab received PBS listing for use in treating wet AMD in 2007 and has since largely replaced bevacizumab for the treatment of AMD in Australia. Although therapy with ranibizumab has been successful, its PBS listing has come at great expense, costing taxpayers $237 million in 2010 (second only to atorvastatin and rosuvastatin).

It is consistent with many of the principles of quality use of medicines (QUM), outlined in the National Medicines Policy,[8,9] for ophthalmologists to select a PBS-listed therapy that has been demonstrated to be safe and effective. But advocates of QUM also emphasise the importance of choosing medicines that are cost-effective for individuals and the community.

A recent study by the US National Eye Institute[10] has raised the question of whether use of ranibizumab can be justified economically. The study compared bevacizumab and ranibizumab for the treatment of wet AMD, administered either monthly or as needed, in 1208 randomly assigned patients. At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity, when administered according to the same schedule. Ranibizumab given as needed, with monthly evaluation, had effects on vision that were equivalent to those of ranibizumab administered monthly. The comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. Differences in rates of serious adverse events were higher with bevacizumab but did not reach statistical significance, and require further study. Results from the second year of this study and from other comparative trials and experiential databases will provide additional information.

Despite this new information having come to light, in Australia there is little motivation for clinicians, the pharmaceutical companies involved, or government bodies to pursue a broader economic agenda. There is no incentive for Australian ophthalmologists or patients to use bevacizumab off-label because the price to the patient for the PBS-listed ranibizumab is only that of the copayment, and the costs for the ophthalmologist visits are the same. There is little incentive for the sponsor of bevacizumab (Roche) to seek a new indication (wet AMD) for this drug — first from the TGA and then from PBAC — because of the substantial costs involved and the doubtful rewards. Also, the relationships between the companies involved appear to militate against moves that might change the present situation. Applications to both the TGA and PBAC are now fully cost-recovered by charges levied on the sponsor of the drug — a unique situation among equivalent developed countries. This provides a considerable disincentive for applications that are primarily in the public interest. While charges can be reduced or eliminated for so-called orphan drugs, this provision would not apply in this case because ranibizumab is currently available and patent-protected.[11] And although it has been suggested that a third party, such as a Royal College, might sponsor an application to the TGA and PBAC in the public interest, this concept has foundered because the sponsor is also responsible for product liability.

This leaves us with the question: what policy options might circumvent the difficulties outlined here and save taxpayers sub-

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stantial amounts of money when treating neovascular AMD with anti-VEGF-A drugs?

First, the drug committees and administrations of public hospitals with significant eye services could recommend off-label use of bevacizumab for AMD, in the light of the National Eye Institute study. Currently, in New South Wales public hospitals, there is no PBS access to ranibizumab. This would also accommodate public patients unable to pay for private ophthalmologist visits. Given the issues with bevacizumab of dose preparation, sterility and shelf life, combining services for efficiency and geographical coverage would make sense, as would amalgamating public clinics that already use bevacizumab off-label for other related indications (eg, diabetic retinopathy).

Second, the government could consider ways in which it could withdraw the PBS listing for ranibizumab for the treatment of wet AMD, on the grounds that treatment with bevacizumab in public eye hospitals is likely to be more cost-effective. This is likely to be problematic for several reasons: the limited capacity of the public sector to provide this treatment; opposition by ophthalmologists operating privately and those who deliver public services; and opposition from the sponsor.

Third, the government could negotiate with Novartis to reduce the cost of ranibizumab, or with Roche to apply to have bevacizumab approved and listed for use in treating AMD. It should be noted that the effort needed to register, list and distribute medicines internationally and in Australia should be considered in these negotiations, but the cost differential now extant in the light of the National Eye Institute study results is no longer defensible.

Finally, the government could accept that it is the only body with the responsibility and capability of acting in the public interest in these matters. The Minister for Health and Ageing could ask the TGA and PBAC to consider listing bevacizumab for neovascular AMD in the public interest, perhaps with a temporary or provisional licence pending accumulation of more data, with the government accepting any liability that may accrue.

Although the challenges of achieving an equitable solution to this problem are considerable, the significance to the PBS budget and subsequently for analogous situations is now a strong incentive for action.

Competing interests

Ken Harvey represented the Chronic Illness Alliance at the Consumers Health Forum PBS Summit. Richard Day is a member of the Ad Hoc Advisory Committee on Drugs in Development for Novartis Australia.

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