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PHARMAC responds on agents to prevent osteoporotic fractures

In this issue of the *Journal*, Dr Nigel Gilchrist (http://www.nzma.org.nz/journal/119-1230/1885) summarises the funding of some medicines that reduce the incidence of osteoporotic fractures. We believe that the current access criteria for alendronate in the treatment of osteoporosis now has the potential to confer considerable population health gains, and that past criteria targeted alendronate so that other areas of health gain were not jeopardised. Discussions with the supplier over raloxifene and PTH are ongoing.

Alendronate

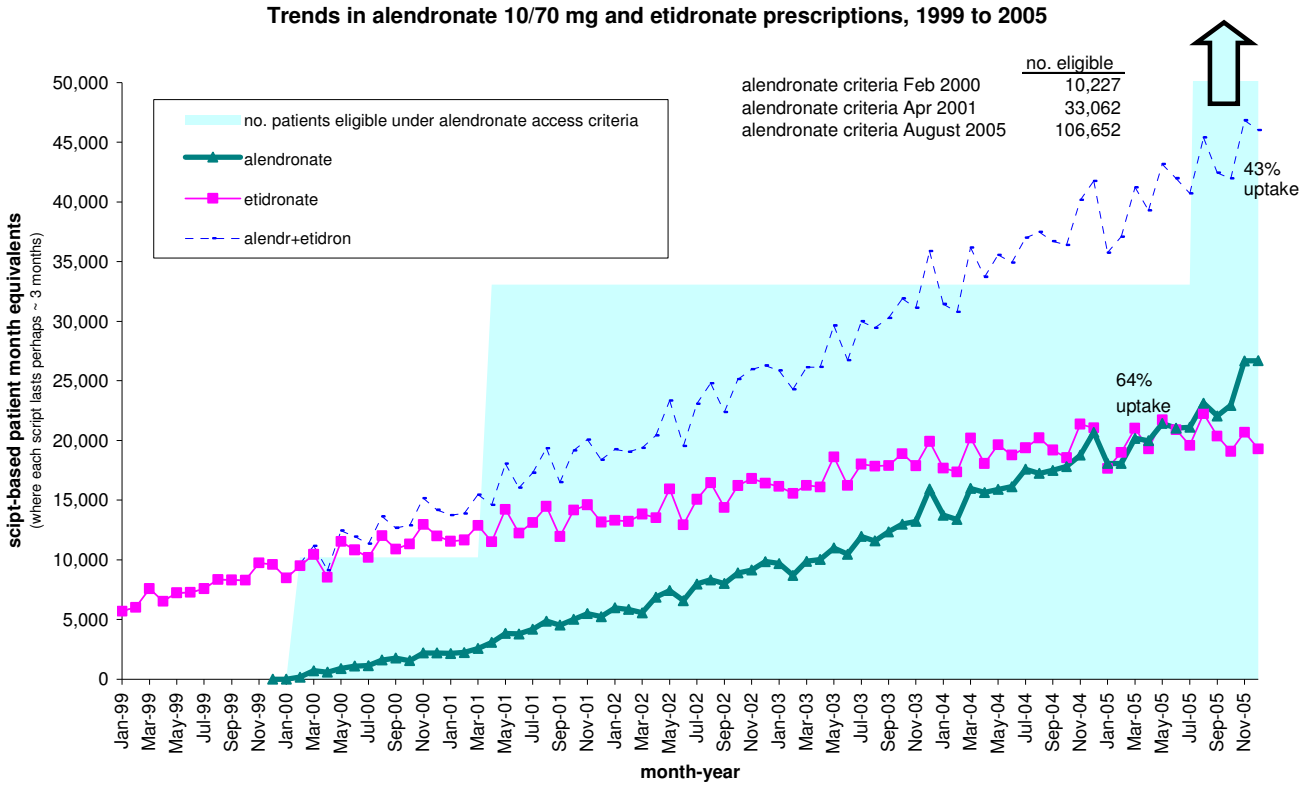
In addition to the other evidence cited for bisphosphonates, the currently-funded bisphosphonates etidronate and alendronate have been shown to halve vertebral fractures (etidronate) and both vertebral and non-vertebral fractures (alendronate) for women with established osteoporosis.[1–3]

We agree that the challenge now is for clinicians to ensure those patients at need now are identified and receive treatment, including falls prevention. Currently there are perhaps 46,000 patients using alendronate or etidronate,[4] when some 107,000 probably meet the new criteria for alendronate[5] (see Figure 1).

The funding of alendronate in the late 1990s for osteoporosis was hampered by its high cost at the time. This translated to an estimated cost of $41,000 per quality-adjusted life year (QALY) and potentially up to $37 million annual cost for the overall target population that was advocated [being women average age 70 years with severe (established) osteoporosis*]. The cost-effectiveness estimate was modelled on a baseline incidence of 3.4% clinically significant hip, wrist or vertebral factures per year, reducing to 1.7% with alendronate—an absolute risk reduction of 1.7% per annum. This compared poorly with other medicine funding options PHARMAC faced at the time.[6]

* i.e. i.e. bone mineralisation density (BMD) ≥ 2.5 standard deviations (SDs) below the mean value in young adults (i.e. a T-score < -2.5 SDs) and one or more previous fragility fracture(s)

Figure 1.



However, for the potential 10,200 patients with very severe osteoporosis [i.e. very low BMD (T-score < -3.0 SDs) and 2+ fragility fractures], funded from February 2000, alendronate's cost-effectiveness, estimated at $3,500 per QALY, was much more favourable. This figure reflected both the greater QALY gains and the hospitalisation and disability support savings elsewhere to the health sector for these patients with higher baseline fracture risks.[7] Extending access in April 2001 by relaxing the previous fracture requirement [i.e. T-score < -3.0 SDs and 1+ fragility fractures] had an estimated cost/QALY of $12,400 for a further potential 22,800 patients.[8]

Full details of PHARMAC's cost-effectiveness analysis at the time can be found at http://www.nzma.org.nz/journal/119-1230/1895/PHARMACTAR9(1999).pdf.[9]

Under the current (October 2005) extended access criteria for alendronate, described by Dr Gilchrist, PHARMAC's preliminary analysis estimated the weighted average cost-effectiveness of widening access to be $1,000 per QALY for fracture risk. This compared well with other medicine funding options available to PHARMAC at the time of the decision. Further details of PHARMAC's analysis can be found at http://www.nzma.org.nz/journal/119-1230/1895/PHARMACTAR70(2005).pdf.[10]

Cost-effectiveness estimates are highly sensitive to the baseline risks of fragility fracture, which in turn vary widely according to BMD, previous fracture history and particularly age[11]—where alendronate becomes less cost-effective in younger age-groups.

By including patients without any previous fragility fracture (but with BMD T-score <- 3.0 SDs), New Zealand's access arrangements for alendronate for the prevention of osteoporosis are now wider that those of Australia.[12]

Raloxifene and PTH

PTAC considered an application for raloxifene to be listed under the same criteria as for alendronate in November 2005. The committee recommended that the application, as presented by the supplier, be declined. PTAC did however consider that raloxifene should be listed on the Pharmaceutical Schedule with a high priority for patients intolerant of bisphosphonates.[13]

Following the widening of access to alendronate last October (which until then had been PHARMAC's priority), and the partly positive recommendation from PTAC for raloxifene, PHARMAC entered into renewed negotiations with Eli Lilly for osteoporosis treatments. We will keep prescribers informed of developments.

PHARMAC is currently funding PTH for two patients under the Exceptional Circumstances scheme. Any proposal for listing PTH on the Pharmaceutical Schedule would need to be targeted to those who would gain most benefit and weighed up against competing medicines.

Comment

In response to some of Dr Gilchrist's specific points, calcitriol was not funded specifically for osteoporosis, and PTAC does not conduct cost utility analyses.

The 1997 recommendations by PTAC and its Osteoporosis Treatments Subcommittee, that alendronate be subsidised for established osteoporosis, need to be placed in context. Both committees considered, at the time (pre-WHI), that hormone replacement therapy (HRT) should be used ahead of alendronate, and that alendronate should only be subsidised for women where HRT was contraindicated or who experienced significant adverse effects after a trial of HRT.[14,15] The Subcommittee had universally agreed that HRT should be used first line and was the preferred treatment based on efficacy, costs and additional benefits in areas other than fractures.[15]

PHARMAC's decision criteria (http://www.pharmac.govt.nz/pdf/opps.pdf) require the consideration of clinical effectiveness, along with cost-effectiveness and seven other criteria. This occurred with PHARMAC's decisions during 1999 to 2001, as it did with the 2005 decision. There is never any temptation to do otherwise – be it with a new chemical entity, or a clinically effective older generic medicine.

PHARMAC's rigour and objectiveness are not new-found. The 1999 technology assessment[9] complied with, yet predated, the formal polices for PHARMAC's economic analyses[16] and guidelines for clinical evidence.[17] Neither PTAC's assessment nor the PHARMAC Board's decision-making processes have changed over that time. What does change is a medicine's place in therapy, its price, the total forecast funds available, and competing areas of health gain from other medicines – all of which affect funding priorities.

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Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. He wrote both the 1999 and the 2005 Technology Assessment Reports for alendronate,[9,10] the 'Recommended methods to derive clinical inputs for proposals to PHARMAC',[17] and co-wrote the 1999 version of PHARMAC's Prescription for Pharmacoeconomics.[16] Tommy Wilkinson and Dilky Rasiah declare no conflicts.

References and Endnotes:

1. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med. 1990;323:73–9.
2. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348:1535–41.
3. Ensrud KE, Black DM, Palermo L, et al. Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. Arch Intern Med. 1997;157:2617–24.
4. PharmHouse data, numbers of scripts for alendronate 10 mg and 70 mg tablets or for etidronate, dispensed during December 2005.
5. PHARMAC estimate based on prevalence and fracture rate data, using methods described in PHARMAC TAR 70[10].
6. Cost-effectiveness estimates varied widely according to baseline fracture risks (in turn exponentially related to age, for instance). These ranged from $11,700/QALY for higher risk patients [women aged ≥70 and BMD <0.59 and multiple vertebral factures and a history of postmenopausal fracture] to $103,300/QALY for lower risk patients [women aged <75 and BMD ≥0.59 and single vertebral fracture and no history of postmenopausal fracture].
7. For patients with T-score <-3.0 SDs and 2+ fragility fractures, PHARMAC models used estimated baseline 7.1% clinically significant factures per year on placebo, reducing to 3.4% with alendronate – an absolute risk reduction of 3.6% fewer clinically-significant fractures per year after rounding.
8. Estimated baseline 5.5% clinically significant factures per year, reducing to 2.7% with alendronate – an absolute risk reduction of 2.8% fewer clinically-significant fractures per year.
9. Alendronate for osteoporosis. PHARMAC Technology Assessment Report No. 9, November 1999.
10. Expanding access to alendronate in the Pharmaceutical Schedule for the treatment and prevention of osteoporosis. PHARMAC Technology Assessment Report No. 70, August 2005.

11. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int. 2005;16:581–9. Epub 2004 Dec 23.

12. For New Zealand's access criteria for alendronate 10 and 70 mg tables, see http://www.pharmac.govt.nz/interactive/scripts/restrict.asp?code=140402+10370101 etc. and http://www.pharmac.govt.nz/interactive/scripts/product.asp?code=140402

    For Australia, see http://www1.health.gov.au/pbs/scripts/dispther.cfm?lvl3id=26944&sched=GA&lvl3name=Drugs%20affecting%20bone%20structure%20and%20mineralization&lvl2name=Drugs%20for%20treatment%20of%20bone%20diseases&lvl1name=Musculo%2Dskeletal%20system

13. PTAC considered that there was a need for a treatment of osteoporosis in patients who could not tolerate an oral bisphosphonate. The Committee considered that raloxifene was less efficacious than alendronate in the treatment of osteoporosis, but may be a suitable alternative if raloxifene could be targeted to patients who were genuinely intolerant to bisphosphonates.

14. Minutes of the Pharmacology and Therapeutics Advisory Committee Meeting 21 February 1997.

15. Minutes of the Osteoporosis Treatments Subcommittee of the Pharmacology and Therapeutics Advisory Committee Meeting 10 June 1997.

16. PHARMAC. A prescription for pharmacoeconomic analysis (version 1), 24 September 1999. A minor update in 2004 (version 1.1) can be found at http://www.pharmac.govt.nz/pdf/pfpa.pdf

17. PHARMAC. Recommended methods to derive clinical inputs for proposals to PHARMAC (version 1B), 20 July 2005. http://www.pharmac.govt.nz/pdf/62465.pdf (referred to at http://www.pharmac.govt.nz/funding_applications.asp)