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PHARMAC responds on TNF inhibitors for inflammatory arthritis

There are several features in the *Special Series* article in October on the funding of tumour necrosis factor (TNF)-alpha receptor antagonists (TNF inhibitors) for inflammatory arthritis (http://www.nzma.org.nz/journal/118-1224/1706/)[1] that deserve clarification.

TNF inhibitors are now funded for severe treatment-resistant rheumatoid arthritis

The PHARMAC Board decided in October 2005 to list the TNF inhibitor adalimumab on the Pharmaceutical Schedule under Special Authority for patients with severe treatment-resistant rheumatoid arthritis (RA). Implementation of this decision was subject to obtaining specific advice from the Pharmacology and Therapeutics Advisory Committee (PTAC). This advice has since been given, and publicly-subsidised adalimumab will be available from 1 January 2006 (http://www.pharmac.govt.nz/pdf/051205.pdf).

Details of eligibility criteria for adalimumab can be found in the Appendix to this letter. New Zealand's criteria will largely align to those of Australia.[2]

PHARMAC has been running a commercial process with suppliers since May 2005, and secured a confidential agreement so that a TNF inhibitor could be listed. The PHARMAC Board resolved to list adalimumab on the basis of all of PHARMAC's nine formal decision criteria (http://www.pharmac.govt.nz/operational_policies_and_procedures.asp).[3] These included the high health needs and lack of other treatment for patients with severe treatment-resistant RA, the effectiveness of TNF inhibitors, and PTAC's high-priority recommendation for funding TNF inhibitors.

Cost-effectiveness of TNF inhibitors for RA

PHARMAC stands behind its previous economic analyses and the discussion document on TNF inhibitors,[4] which was distributed to District Health Board (DHB) hospitals as part of the Hospital Pharmaceutical Assessment Process (HPAP)—detailed later.

The initial document and economic analysis underwent a thorough review process, including internal review of the economic methodology by PHARMAC staff and external specialist rheumatology input. The draft discussion document was then circulated to DHB hospitals for comment. PHARMAC comprehensively considered the responses to this consultation before it made revisions to arrive at the final document. The key elements of all of the consultation responses were also considered by PTAC when it reviewed the economic analysis in August 2004. Issues raised, and PHARMAC's responses to these issues, are detailed in PHARMAC's *Analysis of consultation responses to the Infliximab and Etanercept Discussion Document*, which is available via the link at the corresponding position of the full text version:

http://www.nzma.org.nz/journal/118-1227/1799—note that respondents' identities have been withheld in this version to maintain privacy.

The authors of the *Special Series* article discuss several aspects of the economic analysis, including the target population, the comparator and outcomes used, and what savings are included. We respond as follows:

Target population

The calculations of quality-adjusted life years (QALYs) gained in the economic analysis were relevant to the likely high-need high-response target population in New Zealand, and indeed relate closely to the imminent eligibility (entry and exit) criteria for adalimumab. The calculations were not based on the whole intention-to-treat population in the ATTRACT trial.[5] Rather the analysis was based on unpublished data, sourced from the supplier, on the subgroup of patients in the trial with severe treatment-resistant disease.[4,6] PHARMAC then calculated the $191,000/QALY for infliximab that was specific to this more severely-affected subgroup.

Comparator used in analysis

Methotrexate was the correct comparator to use in PHARMAC's economic analyses. Patients are likely to be on a cocktail of drugs (which all differ in efficacy and side-effects), but in most cases they should be co-administered methotrexate (unless methotrexate is contraindicated or intolerable). Infliximab should be given in combination with methotrexate[7]—and concurrent methotrexate improves the long-term effectiveness of infliximab and etanercept,[8,9] and for adalimumab the best results are obtained with the concurrent methotrexate.[10]

In addition, since methotrexate was used in both arms of the economic analysis (either alone or in combination with infliximab), the cost and benefits occurred in both arms, cancelling out each outer; this in effect was equivalent to comparing infliximab monotherapy with placebo.

PTAC, when reviewing the economic analysis, considered that although methotrexate was not the ideal comparator, it was the most appropriate comparator given currently available data. PTAC members noted that methotrexate was used as the comparator treatment in the key clinical trial on infliximab (ATTRACT), and that there were no data available comparing infliximab with prednisone or leflunomide.

Even if a more expensive agent (e.g. leflunomide) was used as a comparator, it would make little difference to the results of economic analysis—because cost-effectiveness was relatively insensitive to the costs of the comparator treatment (which PHARMAC did vary in sensitivity analysis).

Outcomes considered in analysis

PHARMAC's economic analysis was based on the Health Assessment Questionnaire (HAQ) index scores.[11–13] HAQ scores are considered to be sensitive measures of DMARD effectiveness[14] and correlate with disease severity (ACR scores[15]).[16] HAQ scores were also a pre-specified primary endpoint of the ATTRACT trial.[5]

The use of HAQ scores in the analysis indirectly accounted for empirical reductions in joint damage, as radiological joint destruction strongly correlates with HAQ

scores.[17–21] Therefore, any reductions in joint erosions with TNF inhibitor treatment were reflected in the decrease in HAQ scores and hence the QALY gains measured in PHARMAC's analysis.

The long-term benefits of reducing joint erosion were not measured in the relevant clinical trials. Hence it is difficult to conclusively predict the effects of TNF inhibitors on erosive effects in economic models, other than by using proxy but relevant measures such as HAQ scores.

Savings beyond the health sector

Although there may be non-health sector savings from using TNF inhibitors, there are both philosophical and pragmatic reasons for limiting analyses to health sector costs alone, as outlined by PHARMAC previously in the *Journal*[22] and in its Prescription for Pharmacoeconomics.[23]

Discussion documents sent to DHB hospitals

PHARMAC did not publish the summary discussion document on TNF inhibitors.[4] The document was written in response to a request from DHB hospitals, and made available to all DHBs as part of the HPAP—see http://www.pharmac.govt.nz/hospital_strategy.asp.[24] These documents are circulated to DHBs as confidential documents, at the request of and agreement with the pharmaceutical industry.

The advice in the discussion document[4] should not in itself have been a barrier to DHB hospitals' funding of medicines such as TNF inhibitors. Cost-effectiveness is only one of a number of factors considered by DHBs when making funding decisions about such medicines.

We are interested that concerns with the methods and assumptions used by the economic analysis have been highlighted by international commentators. We would be keen to see the nature or source of these concerns, although we haven't been able to identify them yet in the literature. Being confidential to DHBs, we are unsure how the TNF inhibitors discussion document has gained international readership—beyond overseas rheumatologists working for DHBs on fixed term contracts, whose comments were part of the responses considered by PHARMAC.

Other inflammatory arthropathies

PTAC in November 2004 recommended listing etanercept for ankylosing spondylitis, but with low priority. PTAC did note however that it should reconsider that priority rating once longer-term data become available. In general, applications with low-priority PTAC recommendations are treated with less urgency than higher priority recommendations.[25]

PHARMAC has yet to receive any applications for TNF inhibitors for psoriatic arthritis or other inflammatory arthropathies.

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Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Peter Moodie, Rachel Grocott, and Tommy Wilkinson declare no conflicts.

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3. PHARMAC. Operating policies and procedures of the Pharmaceutical Management Agency ("PHARMAC"), 2nd edition. January 2001. URL: http://www.pharmac.govt.nz/pdf/opps.pdf (Section 2.2 Decision Criteria)
4. PHARMAC. Infliximab (Remicade) and etanercept (Enbrel) for rheumatoid arthritis. Final Hospital Pharmaceutical Assessment summary discussion document no. 12. Wellington, February 2005. Unpublished information for DHB use only.
5. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354:1932–9.
6. This subgroup of those 87 patients in the ATTRACT trial who had severe treatment-resistant disease was restricted to patients with all of the following features: rheumatoid factor positive; had failed three or more alternative DMARDs including methotrexate; had ESR ≥28 mm/hr or CRP ≥20 mg/L (ATTRACT inclusion criteria); and had ≥15 swollen or tender joints.
7. For this subgroup, 40% of patients switched treatment after 14 weeks because they failed to meet the criteria for continuing treatment (being a 50% reduction in the number of swollen and tender joints).
8. Data sheet: Remicade® powder for injection datasheet (infliximab 100mg, Schering-Plough). Medsafe, 2004. URL: http://www.medsafe.govt.nz/DatasheetPage.htm
9. Adalimumab. Prescrire Int. 2004;13:171–5.
10. The TEMPO trial of etanercept found that the ACR responses of patients administered etanercept and methotrexate were significantly better compared with etanercept alone and methotrexate alone. At 52 weeks, 69% of patients in the combination group achieved ACR50, compared with 43% in the methotrexate group (p=0.0091) and 48% in the etanercept group

(p=0.0151). More than a third (35%) of patients receiving combination treatment had disease remission after one year, compared with 16% of patients administered etanercept only and 13% administered methotrexate only. However, a number of patients still had active inflammation. (Klareskog L, van der Heijde D, de Jager JP, et al; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004;363:675–81.)

11. Maini et al 1998 found that patients receiving 1 mg/kg of infliximab without methotrexate became unresponsive to repeat infusions of infliximab. However those who were co-administered methotrexate appeared to benefit from a synergy between the drugs, which was observed as a prolonged duration of response. (Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41:1552–63.)
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14. The HAQ measures both function and pain, by assessing patients' ability to dress, arise, eat, walk, maintain personal hygiene, reach, and grip (degrees of difficulty) and pain (visual analogue scale) (Blumenauer B, Cranney A, Clinch J, Tugwell P. Quality of life in patients with rheumatoid arthritis: which drugs might make a difference? Pharmacoeconomics. 2003;21:927–40.).
15. Scott DL, Strand V. The effects of disease-modifying anti-rheumatic drugs on the Health Assessment Questionnaire score. Lessons from the leflunomide clinical trials database. Rheumatology (Oxford). 2002;41:899–909.
16. American College of Rheumatology (ACR) 20/50/70 system (Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38:727–35.), frequently used in treatment intervention trials.
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22. Scott DL, Pugner K, Kaarela K, et al. The links between joint damage and disability in rheumatoid arthritis. Rheumatology (Oxford). 2000;39:122–32.

23. Metcalfe S, Dougherty S, Brougham M, Moodie P. PHARMAC measures savings elsewhere to the health sector. N Z Med J. 2003;116(1170). URL: http://www.nzma.org.nz/journal/116-1170/362/

    PHARMAC. A prescription for pharmacoeconomic analysis (version 1.1). September 2004. URL: http://www.pharmac.govt.nz/pdf/pfpa.pdf

    The perspective taken by PHARMAC when conducting cost effectiveness analyses is that of the health sector. This relates to PHARMAC's primary objective of achieving the best health outcomes possible from pharmaceutical treatment within the funding available (New Zealand Public Health and Disability Act 2000 [NZPHDA], Section 47 Objectives of Pharmac). This implies that any patient benefits and/or costs that accrue beyond being either healthy or unhealthy are outside the scope of PHARMAC analysis (where "health" is defined by default in the NZPHDA as amenable to health services interventions).

    This means that extra economic production stemming from an individual being healthier is outside the scope of PHARMAC's analyses. Including indirect costs, such as loss of earnings, may prejudice decisions against issues affecting the young, elderly, and less economically productive groups. This conflicts with the public priorities as stated by the Government under the New Zealand Health Strategy (http://www.moh.govt.nz/nzhs.html).

    In addition, indirect costs such as patient travelling times and productivity losses are not easily measured. There is usually little available data on these issues or how to cost them across patient sub-groups. Consequently, incorporating these into analyses would mean using significant and untestable assumptions. Given the large uncertainties involved, PHARMAC has felt it best to avoid incorporating these estimates into its base case analyses.

24. HPAD analyses are undertaken for DHB hospitals as part of the Hospital Pharmaceutical Assessment Process (HPAP). HPAP was established in 2002 as part of the National Hospital Pharmaceutical Strategy, to reduce duplication of work and increase discussion on the costs and benefits of new pharmaceuticals by distributing hospital pharmaceutical assessments nationally. These assessments are distributed to DHBs as confidential documents, which is at the request of and agreement with the pharmaceutical industry.

    Further information on the purpose of HPAP and PHARMAC's role in the distribution of discussion documents can be found on the PHARMAC website—http://www.pharmac.govt.nz/hospital_strategy.asp

25. PHARMAC receives about 30 applications for funding each year. In general, of those applications that PTAC does assign priority to, about 40% have been given high or moderate priority, 30% low priority or fund only if cost-neutral, and for 30% PTAC has recommended they be declined (applications considered by PTAC during 2004 and 2005 to date). Priority ratings are used both to inform PHARMAC on the use of analyst resources in conducting technology assessments and for PHARMAC to prioritise spending.

Appendix

Special Authority criteria for adalimumab, effective from 1 January 2006:

Special Authority for Subsidy

Initial application only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following

1 Patient is an adult who has had severe and active erosive Rheumatoid Arthritis for six months duration or longer; and

2 Treatment is to be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and

3 Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose; and

4 Patient has tried and not responded to at least three months of oral or parenteral methotrexate in combination with at least two of the following (triple therapy): sulphasalazine, prednisone at a dose of at least 7.5 mg per day, azathioprine, intramuscular gold, or hydroxychloroquine sulphate (at maximum tolerated doses); and

5 Patient has tried and not responded to at least three months therapy at the maximum tolerated dose of either:

- 5.1 Cyclosporin alone or in combination with another agent; or
- 5.2 Leflunomide alone or in combination with another agent; and

6 Either

- 6.1 Patient has persistent symptoms of poorly-controlled and active disease in at least 20 active, swollen, tender joints; or
- 6.2 Patient has persistent symptoms of poorly-controlled and active disease in at least four active joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip; and

7 Either:

- 7.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or
- 7.2 C-reactive protein levels not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months;

8 The patient consents to details of their treatment being held on a central registry and has signed a consent form outlining the conditions of ongoing treatment.

Renewal only from a rheumatologist or general physician on the recommendation from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:

9 Treatment is to be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and

10 Either:

- 10.1 Following 4 months initial treatment, the patient has at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
- 10.2 On subsequent reapplications, the patient demonstrates at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician.