Ten years of publicly funded biological disease-modifying antirheumatic drugs in Australia

"There must … be appropriate and proportionate incentives to develop both novel bDMARDs and cost-effective biosimilars"

Summary

- Biological disease-modifying antirheumatic drugs (bDMARDs) for rheumatoid arthritis (RA) treatment were among the first high-cost medicines to be subsidised in Australia.
- High-cost medicines pose several challenges to the Australian National Medicines Policy, which aims to provide timely access to effective medicines at a cost individuals and the community can afford. Thus, novel restriction criteria were developed to encourage cost-effective use of bDMARDs.
- Government expenditure on bDMARD subsidies for RA treatment grew to about $383 million in 2014.
- Evidence that initiation and continuation criteria for bDMARDs meet usually applied cost–benefit criteria is lacking.
- The combined expenditure on tocilizumab, certolizumab pegol and golimumab (added to the Australian Government's Pharmaceutical Benefits Scheme in 2010) was $93 million in 2014, which is 210% over the initial estimate.
- Present and future challenges with regard to bDMARDs for RA and other high-cost drugs include improved expenditure predictions, monitoring of cost-effectiveness in relation to actual use and strategic development, regulation and use of biosimilars.
- Ten years of documentation on clinical and laboratory findings indicating eligibility to initiate and continue on bDMARDs remains un-used. These data represent an untapped opportunity to promote quality of use of bDMARDs and biosimilars and to improve cost predictions for high-cost drugs.

Access to high-cost medicines through the Australian Government's Pharmaceutical Benefits Scheme (PBS) poses a number of challenges for the National Medicines Policy, which aims to provide timely access to medicines at a cost individuals and the community can afford. Biological disease-modifying antirheumatic drugs (bDMARDs) for rheumatoid arthritis (RA) were among the first highly accessed, high-cost drugs to be subsidised in Australia. To restrict their use, a unique subsidy scheme was developed by the Pharmaceutical Benefits Advisory Committee (PBAC), whereby physicians complete written authorities documenting both eligibility to initiate and response to permit continuation.[1] Similar models have been adopted for other high-cost medications (eg, trastuzumab),[2] but there is continuing debate on whether the medicines are available for all who need them, and what constitutes a "worthwhile" response for the individual and for the community who pay.[3,4] In this article, we reflect on bDMARD use and the expenditure for newer bDMARDs for RA (abatacept, tocilizumab, certolizumab pegol and golimumab) (our methods are described in the Appendix). We suggest that an electronic database of data submitted for subsidised bDMARD use could promote the quality use of medicines (QUM) and improve cost expenditure predictions for high-cost drugs.

bDMARDs on the PBS for rheumatoid arthritis

Etanercept and infliximab were PBS listed for RA treatment in 2003, and eight bDMARDs are now available (Box 1). These agents cost between $15 000 and $25 000 per patient per annum, and use has increased such that expenditure was about $383 million in 2014 (Box 2).

Etanercept and adalimumab remain the most commonly prescribed bDMARDs, collectively accounting for 64% of bDMARD use in 2013–2014 (Box 3). The cost of the available bDMARDs on the PBS for RA treatment is relatively uniform, with each bDMARD having been added on a cost minimisation basis compared with a competitor.[5] The dispensing cost for each bDMARD (for the most dispensed item code), and the PBS-reported dispensing price for the maximum quantity, are shown in Box 4.[6]

The subsidy process

In 2003, consultation between stakeholders (the PBAC, pharmaceutical companies, rheumatologists and consumers) resulted in access criteria (to limit access to those for whom less expensive options had been inadequate to achieve acceptable disease activity) and response criteria (based on ACR50 responses [at least a 50% improvement in the American College of Rheumatology score], to ensure only those responding received continued treatment).[1] Limitations to access were also thought warranted given concerns regarding the possibility that bDMARDs might increase the risk of lymphoma. After review, these restrictions were relaxed in 2010 (Box 5).[7] The cost of etanercept and adalimumab has decreased from about $1880 per patient per month in 2003 to $1760 per patient per month in 2014, reflecting a price reduction to achieve a more acceptable cost–effectiveness ratio when the initiation criteria were modified.[7]

After failure of five bDMARDs, no further access to biological agents within a lifetime is allowed,[7] so patients may access two tumour necrosis factor (TNF) blockers and each of the bDMARDs with distinct alternative

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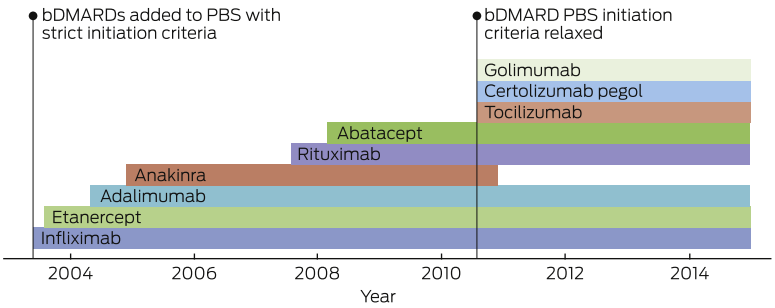
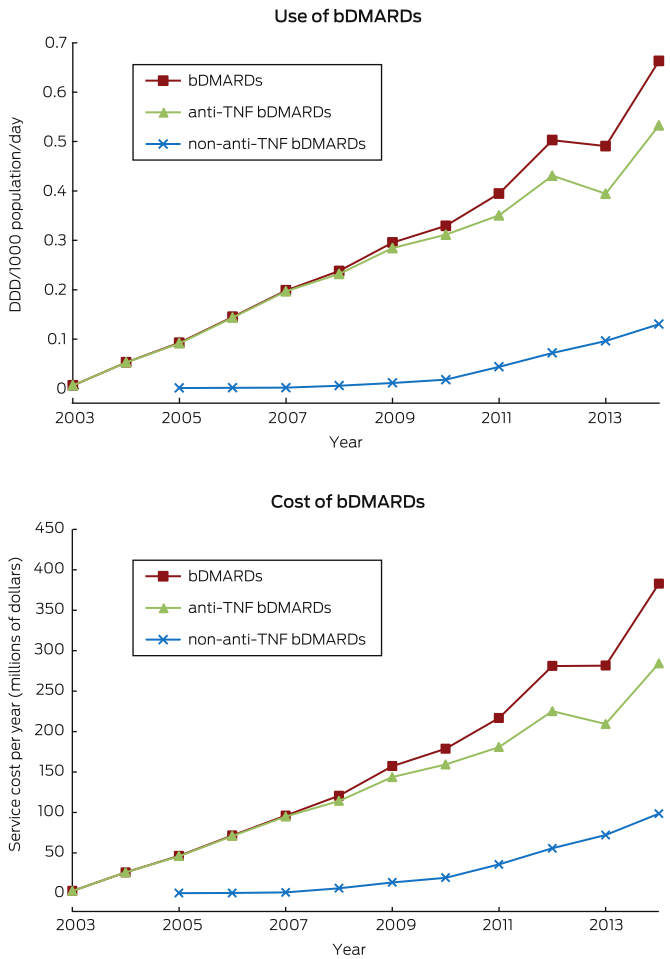
1 Timeline of bDMARD addition and subsidisation for RA on the PBS*



bDMARD = biological disease-modifying antirheumatic drug. RA = rheumatoid arthritis. PBS = Pharmaceutical Benefits Scheme. * Anakinra is an interleukin 1 receptor antagonist that is classified as a "biological response modifier". ◆

2 Use and service cost per year (combined cost to PBS and RPBS) for anti-TNF and non-anti-TNF bDMARDS for treating patients with RA in Australia, 2003–2014*



bDMARD = biological disease-modifying antirheumatic drug. PBS = Pharmaceutical Benefits Scheme. RPBS = Repatriation Pharmaceutical Benefits Scheme. TNF = tumour necrosis factor. RA = rheumatoid arthritis. DDD = defined daily doses. * Anakinra is an interleukin 1 receptor antagonist that is classified as a "biological response modifier"; its use and expenditure has been included in the total bDMARD and non-anti-TNF bDMARD representations above. ◆

actions. The proportion of patients who exhaust all bDMARD options is likely to be small.

Formal evidence that strict initiation and continuation criteria contain gross drug acquisition costs and improve the overall cost–benefit ratio has face validity, but formal proof is lacking and difficult to establish. The need to interpret complex rules and to complete onerous paperwork for access, incidentally or by design, is a disincentive to the promiscuous use of expensive agents. Nonetheless, assessing disease activity at baseline and after defined periods introduces to clinical practice formal assessment of RA disease activity, hitherto reserved for clinical trials. It is thus difficult to argue that such procedures should not be used in routine clinical practice, if for no other reason than to avoid resource expenditure on patients failing to fulfil response criteria and who may benefit from alternative treatment.

Circumventing restrictions

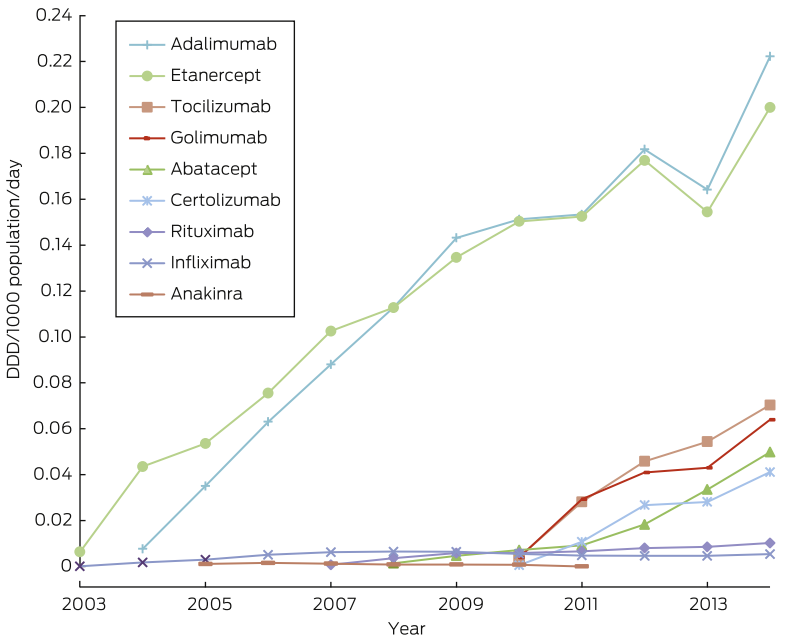
As high disease activity at baseline and subsequent demonstrable clinical response is required for initial and continued bDMARD therapy, concerns are raised regarding those not meeting initiation criteria, or not meeting response thresholds despite improvement.[8] The ethical burden this places on rheumatologists is undefined; however, practices may be altered such that clinicians may be tempted to allow disease activity to increase before applying for bDMARD initiation or bias baseline joint counts.

Expenditure predictions and monitoring

To predict cost-effectiveness and the financial implications of listing a medication on the PBS, usage is estimated before listing,[9] and the difference between estimated and actual usage is serially assessed after listing.[10]

In the 2 years following etanercept and infliximab listing (Box 1), the actual expenditure was $53 million (19% of predicted).[11] This low uptake may have reflected concerns regarding safety, perceived efficacy, availability of the drugs and facilities to administer them, the complexity of the rules, and the administrative burden of applying for initiation and continuation of these agents. Since 2008, abatacept, tocilizumab, certolizumab pegol and golimumab have been introduced, and their use has steadily increased (Box 6). The estimated annual expenditure in the first 5 years for abatacept was $25 million (ie, 50 000 vials at $500 per vial) and less than $10 million for each of tocilizumab, certolizumab pegol and golimumab.[12-15] Expenditure on abatacept was less than predicted for each of the first 5 years, but tocilizumab, certolizumab pegol and golimumab had a combined expenditure of about $93 million for the fifth year of their listing, 210% over the initial estimate. Over the same period, the combined annual expenditure on etanercept and adalimumab rose from about $110 to $227 million. The reasons for the differential uptake of bDMARDs are unclear. Given the lack of head-to-head studies to evaluate the relative efficacy of

3 Use of individual bDMARDs for treating patients with RA in Australia, 2003–2014*



bDMARD = biological disease-modifying antirheumatic drug. RA = rheumatoid arthritis. * Anakinra is an interleukin 1 receptor antagonist that is classified as a "biological response modifier". ◆

bDMARDs, ease of administration and access to appropriate facilities, growing experience with use and the (perceived or actual) benefit of alternative mechanisms of action may be important determinants of choice. Also, the respective marketing strategies of sponsoring pharmaceutical companies are likely to have had an effect.

Cost forecasting for bDMARDs has failed, highlighting the problem with estimations in their current format. It is unclear whether the cost underestimations for tocilizumab, certolizumab pegol and golimumab were due to a larger than expected switch rate, circumvention of restrictions or preference for newer bDMARDs rather than older agents. Recently, European League Against Rheumatism guidelines removed the recommendation that the first-line bDMARD should be a TNF inhibitor, instead stating that there was no preference.[16] However, it does not appear that non-anti-TNF agents (bDMARDs with other mechanisms of action) were strongly preferred, since etanercept and adalimumab use continued to increase. It is also difficult to apportion the effect of changing PBS restrictions in 2010 on anticipated uptake.

The implications of inaccurate expenditure predictions on the National Medicines Policy can be significant. Initiation and continuation criteria are based on clinical trial data and inaccurate predictions could result from difficulty in translating trial evidence to practice. Underestimation of use could be due to a lower than expected commitment or response rates to existing conventional DMARDs and bDMARDs, and this has substantial long-term cost implications. Underestimation could reflect an unforeseen preference for the newer agents (compared with the older, similarly priced biological agents), which could lead to benign cost-shifting. However, the net effect is uncertain, since managed-entry agreements, which share the financial risks of underestimation between funders and sponsors of recently introduced high-cost drugs, are common. The details of such arrangements are not publicly available, and extend beyond the restriction criteria and cost predictions presented herein. For the 2013–14 financial year, the Australian government recovered $500 million from managed-entry agreements and, as such, the importance of inaccurate cost prediction, at least for the

4 Cost of various bDMARDs for treating patients with RA in 2014

bDMARD	Typical maintenance dose	Most dispensed item code (strength)	Dispensed price for maximum quantity*	Total dispensing number	Total expenditure	Cost per dispensing
Abatacept	500–1000 mg IV every 4 weeks (weight based) or 125 mg SC once a week	1221G (4 × 125 mg)	$1754	15 785	$27 559 020	$1746
Rituximab†	1 g IV for 2-dose course; repeat after > 6 months	9544H (1 × 500 mg)	$2033	1847	$8 296 451	$4492
Tocilizumab†	4–8 mg/kg IV every 4 weeks (maximum, 800 mg)	9673D (1 × 400 mg)	$979	12 043	$14 753 071	$1225
Adalimumab	40 mg SC every 2 weeks	9100Y (2 × 40 mg)	$1775	43 820	$77 131 559	$1760
Certolizumab pegol	200 mg SC every 2 weeks	3425G (2 × 200 mg)	$1709	12 330	$20 927 569	$1697
Etanercept	50 mg SC once a week or 25 mg twice a week	9460X (4 × 50 mg)	$1775	31 001	$54 565 851	$1760
Golimumab	50 mg SC once a month	3429L (1 × 50 mg)	$1778	9851	$17 346 793	$1761
Infliximab†	3–7.5 mg/kg IV every 8 weeks	5757B (1 × 100 mg)	$752	1041	$2 426 802	$2331

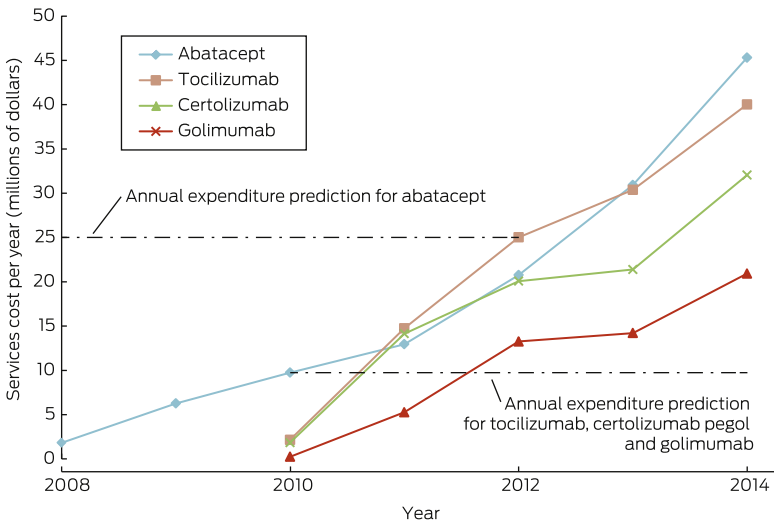
bDMARD = biological disease-modifying antirheumatic drug. RA = rheumatoid arthritis. IV = intravenous. SC = subcutaneous. * Illustrates price to pharmacist for maximum quantity supplied; additional agreed fees may apply.[6] † Although the costs of rituximab, infliximab and tocilizumab appear to differ, like other biological agents they have been added to the PBS on a cost minimisation basis, and therefore apparent cost differences are likely a reflection of different administration frequencies or the need for loading doses.[5] ◆

5 Criteria for PBS-subsidised initiation of a bDMARD for patients with RA

2003 to August 2010	August 2010 onwards
Demonstrably severe active RA* that has failed to achieve adequate response to:	Demonstrably severe active RA* that has failed to achieve adequate response to:
■ methotrexate at a dosage of at least 20 mg weekly; and	■ 6 months of intensive DMARD treatment, which must include:
■ methotrexate (at a minimum dosage of 7.5 mg weekly), in combination with two other DMARDs for a minimum of 3 months; and	► 3 months of consecutive treatment with methotrexate at a dosage of at least 20 mg weekly (unless contraindicated); and
■ Leflunomide, cyclosporin or leflunomide with methotrexate for a minimum of 3 months	► 3 months of one of sulfasalazine, hydroxychloroquine or leflunomide at an effective dose

PBS = Pharmaceutical Benefits Scheme. bDMARD = biological disease-modifying antirheumatic drug. RA = rheumatoid arthritis. DMARD = disease-modifying antirheumatic drug. * Based on number of joints that are both swollen and tender (> 20 in total or four large joints) and one or more elevated inflammatory markers (erythrocyte sedimentation rate > 25 mm/hour or C-reactive protein level > 15 mmol/L). ◆

6 Service cost per year (combined cost to PBS and RPBS) to provide abatacept, tocilizumab, certolizumab pegol and golimumab to patients with RA, and predicted cost per year based on 5 years of use in RA, 2008–2014



PBS = Pharmaceutical Benefits Scheme. RPBS = Repatriation Pharmaceutical Benefits Scheme. RA = rheumatoid arthritis. ◆

duration of these agreements, is uncertain.[17] It is likely that price-capping agreements were in place for abatacept, tocilizumab, certolizumab pegol and golimumab throughout the investigated period, although details of recovered monies are not available.[2]

Biosimilars

Recently, biosimilars of etanercept and infliximab have offered promise for providing less expensive bDMARDs. Unlike small-molecule generic products that can lower price by as much as 90%, biosimilars have more complex development processes which result in post-translational modifications in structure. Typically, prices are 20%–30% lower than branded products.[18] These factors can result in reluctance to switch from branded products that are "known" to work.[18] However, clinicians and sponsors may be placing too strong an emphasis on post-translational differences, as branded agents can also exhibit functionally and/or immunologically important post-translational modifications over time.[19] The price of a branded bDMARD undoubtedly includes a substantial profit margin to compensate for development costs. A biosimilar, however, can be developed in the knowledge that it is directed at an appropriate target. There must, therefore, be appropriate and proportionate incentives to develop both novel bDMARDs and cost-effective biosimilars. There is a need for regulatory agencies, funders and manufacturers of reference and biosimilar agents to strive to assemble clinical research data, and to achieve funding arrangements which increase access to the most effective biological products (be they branded or biosimilar) at a time when they will be most effective. Without this collaborative action, we may not see a substantial reduction in the cost of newer bDMARDs until patents expire on the small-molecule tyrosine kinase inhibitors that are not yet marketed for the treatment of RA in many countries.[20]

Future perspectives

A key feature of Australian programs for access to high-cost drugs is the need to provide clinical data before initiation and when evaluating response. These data could be used to examine real-world effectiveness and review expenditure predictions, with a view to developing better predictive models; however, these data have been inaccessible to date.[1,21]

Recent advents to allow access to a 10% sample of individualised PBS data are a step towards improved QUM monitoring. Yet, a real-world database of clinical and laboratory data could also have an important role. The information would, however, lack patient-reported data and quality-of-life outcomes. These shortcomings could be addressed in part by linkage with the Australian Rheumatology Association Database, which contains this information for a subset of the population.[22] A real-world database would also present a potentially novel framework for nationwide research projects that could, for example, investigate the clinical utility of pharmacogenomic and therapeutic drug monitoring variables as a means to optimise bDMARD selection. It would have the potential to answer questions about bDMARD use that have remained unanswered over the past 10 years, some of which are listed in Box 7.

Like the novel bDMARDs introduced before them, bDMARD biosimilars will be among the first high-cost agents in their class to be publicly funded, and the developed funding models will lay the framework for accessing and pricing biosimilars in the future. Since their

7 Example questions to be addressed by a real-world database of restriction criteria data

Questions
What is the response to each bDMARD when prescribed according to current restriction criteria? Do any factors explain variance among patient populations?
Is the cost-effectiveness of bDMARDs, prescribed according to current restriction criteria, comparable with that predicted from trial data?
How do access and response to bDMARDs in remote areas compare with access and response in other areas? What is the differential between private versus public sector access and response?
How many patients have switched to the newer bDMARDs and is this due to documented failure?
What concomitant treatments are patients on bDMARDs receiving (eg, corticosteroids, conventional DMARDs), and do they affect response rates?
Are the response rates for biosimilars equivalent to that for the originator?
What is the impact on immunogenicity of changing between an originator and multiple biosimilar bDMARDs?

bDMARD = biological disease-modifying antirheumatic drug. DMARD = disease-modifying antirheumatic drug. ◆

introduction is likely to result in only modest price reductions, relaxation of access criteria is unlikely unless acceptable reductions in cost–effectiveness ratios can be demonstrated. Funding of medicines currently relies on substantial cost reduction following the introduction of generics, which frees up funds that can be directed towards new medicines.

In this article, we have used bDMARDs to exemplify current and future challenges to achieving equitable access to high-cost drugs. A real-world database could also inform questions regarding effectiveness and appropriate access of other high-cost drugs that use similar written authority-based prescribing models. In turn, these data could inform future negotiations regarding what constitutes a fair price for the benefit accruing from the use of these agents.

Conclusion

The use of bDMARDs to treat RA, and the cost to taxpayers, has steadily increased in Australia since 2003. Despite the newer bDMARDs, etanercept and adalimumab remain the two most used agents. The impact of strict initiation and continuation rules on overall expenditure is uncertain, but is likely to have lessened as prescribers have become more familiar with procedures. Prediction of expenditure on newly introduced high-cost drugs remains inaccurate despite substantial experience with the systems for restricted access. Present and future opportunities that must be explored to ensure that the goals of the National Medicines Policy are met include the strategic development, regulation and use of biosimilars. These endeavours should include analyses of authority prescription data which have been collected over the past 10 years and continue to be collected with the objectives of refining access and improving cost–effectiveness ratios.

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