Patterns in use and costs of conventional and biologic disease-modifying anti-rheumatic drugs in Australia

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Abstract

Objective

The aim of this study was to characterise the use and costs of subsidising conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs in Australia from 2004-2014 through pharmaceutical benefits schemes.

Methods

Dispensing and expenditure data on conventional and biologic DMARDs were extracted from Medicare Australia and temporal trends were analysed. Medicine use was standardised in terms of the defined daily dose (DDD) per 1,000 population per day (DDD/1,000 population/day).

Results

Conventional and biologic DMARD use increased 74% over the study period (4.86 to 8.46 DDD/1,000 population/day; average annual increase 6.7%). Conventional DMARDs accounted for the vast majority of total use and increased 55% (4.81 to 7.43 DDD/1,000 population/day), while biologic DMARD use increased 1,784% (0.055 to 1.030 DDD/1,000 population/day). The most frequently used conventional DMARD was methotrexate (56% total conventional DMARD use) and use increased 95%. Hydroxychloroquine and leflunomide use increased marginally while sulfasalazine use declined 4.2%. Etanercept was the most commonly used biologic DMARD in 2004 and adalimumab in 2014. Conventional DMARD expenditure decreased 4.2% to AUD$33.3 million but biologic DMARD expenditure increased 2,089% to AUD$585.4 million.

Conclusion

The use of conventional and biologic DMARDs increased substantially over a decade in Australia. Patterns of use of conventional DMARDs have changed, and costs have decreased. In contrast a significant escalation in both the use and cost of biologic DMARDs has occurred. Further research is required to address cost-effectiveness, regulation and quality use of these medicines in clinical practice.

Key words

disease-modifying anti-rheumatic drugs, biologic disease-modifying anti-rheumatic drugs, utilisation, rheumatoid arthritis, pharmaceutical benefits scheme

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Introduction

Pharmacological agents are integral to the management of many systemic autoimmune conditions and particularly those with associated inflammatory joint disease. Conventional disease-modifying anti-rheumatic drugs (DMARDs) and newer biologic DMARDs are indicated for conditions such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

In order to ensure timely and affordable access, these medicines are available to patients in Australia through the Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme. The Australian Government subsidises the cost of each prescription that is dispensed and patients contribute a general or concessional co-payment. Data on subsidised prescriptions are recorded.

Drug utilisation can be accessed through calculation of the defined daily dose (DDD) per 1,000 population per day (DDD/1,000 population/day) using World Health Organisation methodology (1). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (1). Use of such a method facilitates comparison between different medicines and international drug consumption patterns (1).

There is limited published data regarding the utilisation and costs of conventional DMARDs in Australia (2). The use of the biologic DMARDs for inflammatory joint diseases, and the impact of these high cost medications on the pharmaceutical benefits schemes has not been examined as a whole since 2007 (3), only four years after benefits scheme listing of the first biologic. The aim of this study was to characterise the use and costs of subsidising conventional and biologic DMARDs indicated for RA, AS and PsA in Australia between 2004 and 2014.

Materials and methods

Data collection

Conventional and biologic DMARDs that had been listed on the Australian Pharmaceutical Benefits Scheme or Repatriation Pharmaceutical Benefits Scheme from January 2004 onwards were examined, this included seven conventional and nine biologic DMARDs. Each medicine was indexed by a unique item code according to strength, formulation, and clinical indication. Conventional DMARD general usage and biologic DMARD usage exclusive to RA, PsA and AS treatment was captured where possible using benefit scheme item codes. All biologic DMARD formulations are benefit scheme authority items and may only be prescribed by a rheumatologist or clinical immunologist according to stringent therapeutic criteria for RA, PsA and AS (3). Of the conventional DMARDs, leflunomide requires specialist authorisation, so use in RA and PsA can be identified by benefit scheme item codes. Auranofin and sodium aurothiomalate are solely indicated in RA according to the Australian Medicines Handbook (4). The remaining conventional DMARDs may be prescribed in other autoimmune diseases and therefore the results for conventional DMARDs characterise total usage. Methotrexate is listed under two Anatomical Therapeutic Chemical codes on the benefit schemes (5). Only orally administered methotrexate was examined as the other indication is for treating cancer (L01BA01) and was therefore excluded (5).

Data analysis

Data on conventional and biologic DMARD subsidised prescriptions were extracted from Medicare Australia (6). Reports on services (number of subsidised prescriptions dispensed) and benefits (cost to government) for the calendar years 2004–2014 were generated using Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme item codes. Drug utilisation was calculated in defined daily dose (DDD) per 1,000 population per day (DDD/1,000 population/day) using World Health Organisation methodology (1). There was no DDD for rituximab as it is primarily used for neoplastic disease treatment in highly variable and individualised dosage ranges. The Australian Medicines Handbook recommended dosage of rituximab for RA was therefore used to estimate a DDD

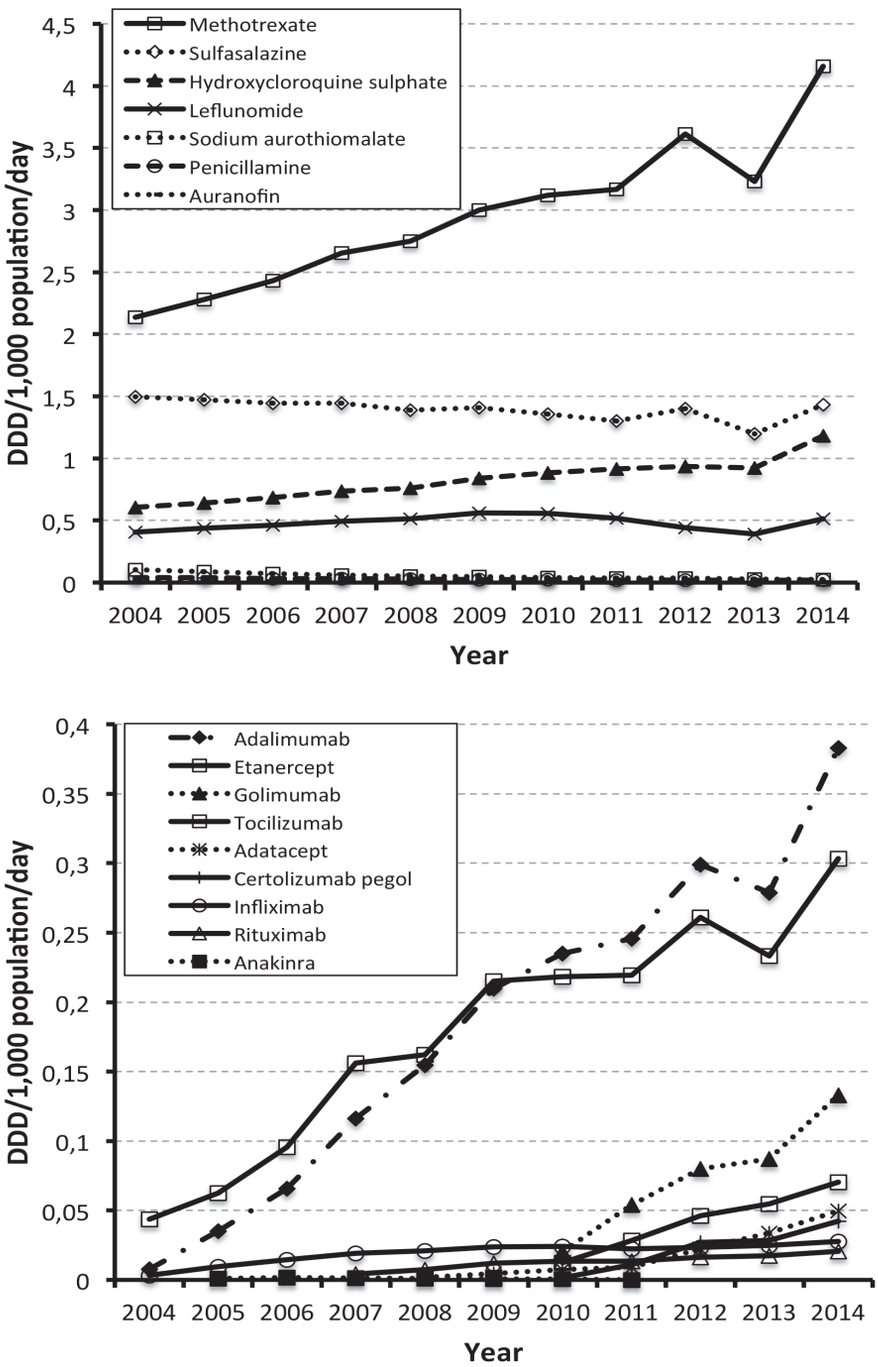

Fig. 1. Dispensed use (DDD/1,000 population/day) of individual conventional (upper panel) and biologic DMARDs (lower panel) in RA, AS and PsA patients in Australia through the benefit schemes from 2004-2014.

age yearly dose an RA patient would receive and dividing it by 365.25 days) (4). Mid-year population data were obtained from the Australian Bureau of Statistics (7). An appropriate adjustment was made when items were not subsidised for a full calendar year. Four conventional DMARD items were priced under the general patient co-payment at some point during the general beneficiaries were not available. The use of these four DMARD items under general beneficiaries was approximated by considering the proportions of general beneficiaries in the six years prior to the price decrease under the co-payment. No adjustments were made to account for economic inflation. Ethics approval was not required as the data were publically available and de-identified. All data were analysed using Microsoft Office Excel 2011.

Results

Total Australian consumption of conventional and biologic DMARDs increased 74% from 4.86 to 8.46 DDD/1,000 population/day between 2004 and 2014 (average annual increase 6.7%). Conventional DMARDs accounted for the vast majority of total use and increased 55% from 4.81 to 7.43 DDD/1,000 population/day (5.0% average annual increase). Methotrexate was the most frequently used conventional DMARD with 56% of total conventional DMARD use in 2014 (Fig. 1). Methotrexate use increased 95% from 2.14 DDD/1,000 population/day in 2004 to 4.16 DDD/1,000 population/day in 2014, including adjustments for general patient prescriptions priced under the general co-payment. Use of hydroxychloroquine and leflunomide increased slightly from 0.61 and 0.41 DDD/1,000 population/day in 2004 to 1.18 and 0.60 DDD/1,000 population/day in 2014, respectively, whilst sulfasalazine consumption declined 4.2% (1.50 in 2004 to 1.43 DDD/1,000 population/day in 2014). Use of gold salts and penicillamine was low at the beginning of the study period and further decreased over time indicating limited use.

There was a 1,784% increase in the use of biologic DMARDs over the study period, with a 162% average annual increase from 0.055 in 2004 to 1.030 DDD/1,000 population/day in 2014. Etanercept was the most frequently used biologic DMARD in 2004, but then moved to second after adalimumab from 2010 onwards (Fig. 1). These two medicines consistently represented two thirds of biologic DMARD use (67% of all biologic DMARD use in 2014). Adalimumab use increased 4,872% from 0.008 in 2004 to 0.383 DDD/1,000 population/day in 2014 (443% average annual increase). With the exception of anakinra, which was delisted from the benefit schemes in 2010, use of all other biologic DMARDs increased over the study period.

Total government expenditure on conventional DMARDs decreased 4.2%

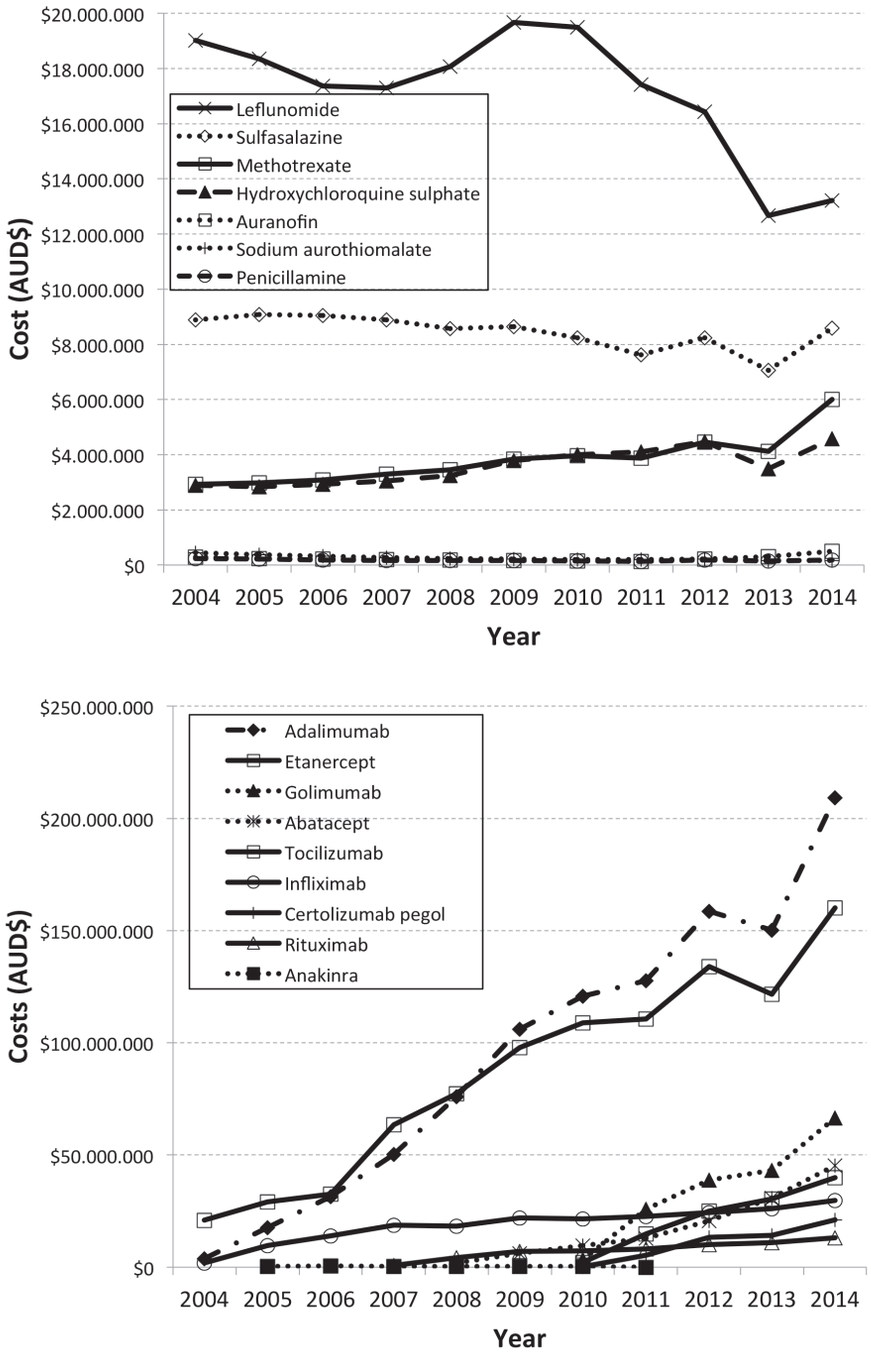

Fig. 2. Costs (AUD$) of individual conventional DMARDs (upper panel) and biologic DMARDs (lower panel) in RA, AS and PsA patients in Australia through the benefits schemes from 2004-2014.

from AUD$34.7 million in 2004 to AUD$33.3 million in 2014. The costs of the individual medicines sodium aurothiomalate, leflunomide, penicillamine and sulfasalazine decreased steadily over the study period, while costs of auranofin, hydroxychloroquine and methotrexate increased slightly (Fig. 2). In 2014, conventional DMARDs represented only 5% of the total cost of both conventional and biologic DMARDs. Total cost to government of biologic DMARDs increased 2,089% from AUD$26.7 million in 2004 to AUD$585.4 million in 2014 (190% average annual increase). Adalimumab and etanercept combined, accounted for 63% of biologic DMARD expenditure for RA, AS and PsA in 2014, at $209.3 million and $160.2 million respectively. The subsidy of new biologic DMARDs in recent years contributed to increasing costs over the study period for example golimumab subsidised through the benefits schemes from 2010 increased in use by 552% over four years and in expenditure by 1,916% from AUD$3.3 million in 2010 to AUD$66.6 in 2014.

Discussion

This study is the first to examine the dispensed use and government costs of both conventional and biologic DMARDS in Australia over an eleven-year period. It updates and expands on previous studies (2, 8). The increase in total use (74%) exceeded the population increase (18% to 23.5 million people) over the decade (7). Globally, the prevalence of inflammatory joint diseases such as RA have remained relatively unchanged from 1990 to 2010 and Australian estimates are unlikely to have changed during our study period (3, 9). This study captured complete dispensed use and cost data for all subsidised conventional DMARDs and biologic DMARDs (for RA, AS and PsA) in Australia from 2004 to 2014. Calculation of DDD/1,000 population/day allows comparison of individual medicines and evaluation of temporal trends. This study however has some limitations. Collection of aggregated data does not allow dispensed use to be linked to individual patient diagnoses, characteristics (*e.g.* age, sex or disease severity) or treatment (*e.g.* monotherapy or combination therapy). Medicare does not record data on private prescriptions, items priced under the general patient co-payment (*i.e.* for general patients) and inpatient hospital use. Use in these categories however is likely to be small. There was no DDD for rituximab in RA as its primary indication is neoplastic disease. We calculated a DDD for RA treatment based on Australian dosing guidelines, which may differ from doses used elsewhere. The specific indication for use of some DMARDs (methotrexate, sulfasalazine, hydroxychloroquine and penicillamine) could not be determined. They may be used in other autoimmune diseases but the estimated prevalence of these is low compared to the prevalence of RA, AS

and PsA (3). Of interest, there was a decrease in dispensed use and costs for all medicines in 2013. The reason is unknown but anecdotal evidence suggests an issue with government data collation in the Medicare database.

General trends in the use of conventional DMARDs between 1992 and 2004 (2) continued throughout the subsequent decade to 2014. The dispensed use of methotrexate in Australia is comparable to studies in Europe. A population-based Finnish study found methotrexate was prescribed to 69% of newly diagnosed patients with RA in 2006-07; a slight increase from previous years (10). In the US, methotrexate was prescribed to half (49%) of RA patients in 2009 in rheumatology practices participating in a longitudinal (1983–2009) cohort study (11). Hydroxychloroquine was second to methotrexate (30%) in 2009 whilst leflunamide use was 13% and sulfasalazine use was 7%. Another US study found a significant increase in the use of methotrexate both as a first-line agent for newly diagnosed RA and as part of an established regimen in a veterans population between 1999 and 2009 (12). This coincided with decreased use of sulfasalazine and hydroxychloroquine as initial therapy.

Hopkins *et al*. recently published a review of biologic DMARD use in Australia for RA alone and demonstrated significantly increased usage and the corresponding growth of government expenditure to AUD$383 million in 2014 (8). The increased use of biologic DMARDs was also seen in a five-year observational cohort study of Australian RA patients from 2009–2014 (13). This study linked medicine use with disease activity. The proportion of patients taking a biologic DMARD increased over time across all levels of disease severity. In 'remission' patients, treatment with a biologic DMARD more than doubled from 17% in 2009 to 37% in 2014 (13). Use of the biologic DMARDs for RA including adalimumab, etanercept and infliximab was slightly higher in Ireland, the Netherlands, Norway and Portugal than Australia between 2003 and 2007 (14-16). It ranged from 0.32 (Portugal) to 1.89 (Norway) DDD/1,000 population/day for the three drugs combined, compared with 0.20 DDD/1,000 population/day for the same year in Australia. An increase in adalimumab, etanercept and infliximab use over time was observed in all four European countries.

Combined with the high and increasing use seen internationally, it is likely the use of biologic DMARDs will further increase. The costs to government are growing rapidly, with adalimumab and etanercept (all indications) in the top five medicines with the highest cost to government (others are high volume medicines such as rosuvastatin, atorvastatin and esomeprazole). Indeed, government spending in the 2013–2014 financial year on immunosuppressants ($743.7 million) was more than double that of antineoplastic agents ($292.2 million) (17).

The biologic DMARDs are a burgeoning cost to the benefit schemes in Australia. These medicines were originally subsidised based on the results from pivotal trials and acceptable cost effectiveness analyses (18). There has been little subsequent evidence about how well these medicines work in real world patients. A recent study involving 1403 patients from a single outpatient clinical suggested that the risk of adverse effects amongst rheumatoid arthritis patients treated with biological DMARDs was significantly higher compared to those treated with conventional DMARDs (19). A further government report concluded that biological DMARDs were not cost-effective at their unit prices in 2009 (18). The first oral biologic DMARD (tofacitinib citrate) was subsidised in 2015 for severe active RA on a cost-minimisation basis compared to adalimumab (20). Listing of biosimilar medicines also has the potential to reduce benefit scheme expenditure on biologic DMARDs by approximately 20%–30% (21).

Ensuring a balance between the optimal clinical use of biologic DMARDs at a sustainable cost to the payer is crucial for policy-makers and patients alike in Australia and across the world. Further research linking medicine use to health outcomes, safety and cost-effectiveness is crucial.

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References

1. WHO Collaborating Centre for Drug Statistics Methodology. Norwegian Institute of Public Health; 2009 [updated 2009 December 17; cited 2015 March 27]; Available from: https://www.whocc.no
2. CHAN V, TETT SE: Changes in use of disease-modifying anti-rheumatic drugs in Australia over the period 1992-2004. *Pharmacoepidemiol Drug Saf* 2006; 15: 462-8.
3. Australian Institute of Health and Welfare: The use of disease-modifying anti-rheumatic drugs for the management of rheumatoid arthritis. Canberra: AIHW; 2011 [updated 2015; cited 2015 March 17]; Available from: http://www.aihw.gov.au/publication-detail/?id=10737418554
4. Australian Medicines Handbook Pty Ltd. Australian Medicines Handbook 2015 (online). Adelaide2015 [cited 2015]; Available from: http://amhonline.amh.net.au/
5. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015. WHO; 2015 [updated December 19, 2013; cited 2015 April 19]; Available from: http://www.whocc.no/atc_ddd_index/
6. Australian Government Department of Human Services. Pharmaceutical Benefits Schedule Item Reports. Medicare Australia Statistics; 2015 [updated March 25, 2015; cited 2015 March]; Available from: http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp
7. Australian Bureau of Statistics. Table 4: Estimated Resident Population, States and Territories (Number) 2015; Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Jun%202014?OpenDocument
8. HOPKINS AM, PROUDMAN SM, VITRY AI, SORICH MJ, CLELAND LG, WIESE MD: Ten years of publicly funded biological disease-modifying antirheumatic drugs in Australia. *Med J Aust* 2016; 204: 64-8.
9. CROSS M, SMITH E, HOY D *et al*.: The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014; 73: 1316.
10. RANTALAIHO V, KAUTIAINEN H, VIRTA L, KORPELA M, MÖTTÖNEN T, PUOLAKKA K: Trends in treatment strategies and the usage of different disease-modifying anti-rheumatic drugs in early rheumatoid arthritis in Finland. Results from a nationwide register in 2000-2007. *Scand J Rheumatol* 2011; 40: 16-21.
11. KIM SC, YELIN E, TONNER C, SOLOMON DH: Changes in use of disease-modifying antirheumatic drugs for rheumatoid arthritis in the United States during 1983-2009. *Arthritis Care Res* 2013; 65: 1529-33.
12. NG B, CHU A, KHAN MM: A retrospective cohort study: 10-year trend of disease-modifying antirheumatic drugs and biological

agents use in patients with rheumatoid arthritis at Veteran Affairs Medical Centers. *BMJ Open* 2013; 3.
13. LITTLEJOHN G, ROBERTS L, BIRD P *et al*.: Patients with rheumatoid arthritis in the Australian OPAL cohort show significant improvement in disease activity over 5 years: a multicenter observational study. *J Rheumatol* 2015; 42: 1603-9.
14. HOEBERT JM, MANTEL-TEEUWISSE AK, VAN DIJK L, BIJLSMA JWJ, LEUFKENS HGM: Do rheumatoid arthritis patients have equal access to treatment with new medicines? Tumour necrosis factor-alpha inhibitors use in four European countries. *Health Policy* 2012; 104: 76-83.
15. MAHIC M, SKURTVEIT S, SELMER R, RONNING M, FURU K: Prevalence, incidence and persistence of etanercept and adalimumab in Norway 2005-2009. *Pharmacoepidemiol Drug Saf* 2011; 20: 457-63.
16. HOEBERT JM, MANTEL-TEEUWISSE AK, VAN DIJK L, LAING RO, LEUFKENS HG: Quality and completeness of utilisation data on biological agents across European countries: tumour necrosis factor alpha inhibitors as a case study. *Pharmacoepidemiol Drug Saf* 2011; 20: 265-71.
17. Pharmaceutical Benefits Scheme. Expenditure and Prescriptions twelve months to 30 June 2014. Australian Government Department of Health; 2015 [cited 2015 March 15]; Available from: http://www.pbs.gov.au/statistics/2013-2014-files/expenditure-and-prescriptions-12-months-to-30-june-2014.pdf
18. Pharmaceutical Benefits Scheme. PBAC Review of bDMARDs for the treatment of severe active rheumatoid athritis. Australian Government Department of Health; 2009 [cited 2015 March 14]; Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-12/pbac-psd-bdmards-dec09
19. LAMPROPOULOS CE, ORFANOS P, BOURNIA V *et al*.: Adverse events and infections in patients with rheumatoid arthritis treated with conventional drugs or biologic agents: a real world study. *Clin Exp Rheumatol* 2015; 33: 216-24.
20. Pharmaceutical Benefits Scheme. Public Summary Document - March 2015 PBAC Meeting: 5.24 Tofacitinib. Canberra2015 [updated 3 July 2015; cited 2015 23 July]; Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/tofacitinib-psd-march-2015.pdf
21. Australian Government Department of Health. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee. Canberra: Department of Health; 2015 [cited 2015 July 4]; Available from: http://www.pbac.pbs.gov.au