

ORIGINAL ARTICLE

Effect of treatment with biological agents for arthritis in Australia: the Australian Rheumatology Association Database

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Key words

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Abstract

Background: The Australian Rheumatology Association Database (ARAD), a voluntary national registry, has been established to collect health information from Australian patients with inflammatory arthritis for the purpose of monitoring the benefits and safety of new treatments, in particular the biological disease-modifying anti-rheumatic drugs (bDMARDs). These drugs are proving to be very effective, yet little is known of their long-term effectiveness or safety. Patient registries that systematically gather data on large cohorts of unselected patients are increasingly believed to be an essential means of answering questions of the long-term effectiveness and safety of new drugs. The aim of this report is to describe the role, development and structure of ARAD and provide some preliminary data.

Methods: As of 1 August 2006, 563 patients with rheumatoid arthritis prescribed a bDMARD have been enrolled in ARAD, involving 105 rheumatologists from across Australia.

Results: The data collected will enable examination of multiple domains of patient responses to bDMARDs, including quality of life, health-care utilization, incidence of adverse events and the effects of therapy switching.

Conclusion: Evidence-based information about the long-term outcome of bDMARD therapy is essential for clinicians, consumers, policy-makers, drug development companies and approval agencies, to enable better care and improved outcomes for patients with inflammatory arthritis.

Introduction

The Australian Rheumatology Association (ARA) has recently established the Australian Rheumatology Association Database (ARAD). The database collects health information from Australian patients with inflammatory arthritis for the purpose of monitoring the benefits and safety of new treatments, in particular, the biological disease-modifying anti-rheumatic drugs (bDMARDs). Its initial development was funded by unconditional educational grants to the ARA from pharmaceutical companies involved with new therapies for arthritis including the

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Potential conflicts of interest: None

bDMARDs. Since 2006, the maintenance and further development of ARAD is also funded by a National Health and Medical Research Council Enabling Grant (Number 384330) and Monash University. The database is endorsed by the ARA, participation is voluntary, and at August 2006, 105 (41.7%) of Australian rheumatologists and 563 patients were contributing data. Here, we outline the reasons for establishing the database focusing on rheumatoid arthritis (RA); issues related to its implementation, some early outcomes and comparisons with other national registries specifically designed to monitor the benefits and/or safety of new arthritis treatments.

Reasons for establishing ARAD

RA is a chronic, autoimmune, inflammatory joint disease of unknown cause, which results in progressive and irreversible joint damage.¹ It is associated with premature death and reduces quality of life and physical, social and emotional functioning.²⁻⁴ The peak onset is in the fourth and fifth decades⁵ and so affects the individuals in their peak income-earning years resulting in high work disability.⁶ In Australia, 2.4% of the population report having RA.⁷ Minimizing the effect of this disease is an Australian health-care priority.⁸

New therapies for RA

There is currently no cure for RA and no known method of prevention. Successful management involves arresting or controlling progression of the disease through early diagnosis and early introduction of disease-modifying anti-rheumatic drugs (DMARDs).⁹ Up until recently, the mainstay of DMARD therapy has been drugs, such as methotrexate and salazopyrine with a long history of use and consequently a well-known risk profile. However, over recent years, new drugs including leflunomide and bDMARDs such as the tumour necrosis factor (TNF)- α -inhibitors etanercept, infliximab and adalimumab, and anakinra, an IL-1Ra analogue, have been introduced into clinical practice with the anticipation that they are a significant breakthrough in terms of altering the course and prognosis of RA. Although evidence for their short-term efficacy is well established from randomized controlled trials (RCT), there have been concerns raised about their short-term safety.¹⁰⁻¹³ For example, a recent meta-analysis of nine placebo-controlled clinical trials of infliximab and adalimumab found a 2.0-fold (95% confidence interval (CI) 1.3-3.1) increased risk of serious infections regardless of bDMARD dose and the risk of malignancy was increased 4.3-fold (95% CI 1.6-11.8) among patients receiving the higher dose schedules.¹⁴ However, these risk estimates for developing adverse events need to be inter-

preted cautiously in view of the short follow-up periods (limited to the duration of the trials), the low rate of malignancy in the control arms of the trials and some disparity between these results and those reported in long-term health registries.¹⁵⁻¹⁷ Although not evaluated in the meta-analysis, an increased incidence of malignancies has also been reported to be associated with the use of etanercept, the most commonly prescribed bDMARD in Australia, in patients with Wegener's granulomatosis.¹⁸

Long-term safety of bDMARDs

The bDMARDs are not cures and need to be given indefinitely. In addition to being costly (> A\$20 000 per patient per year), this also raises concerns with respect to their long-term safety.¹⁹ Long-term effects cannot be anticipated from preclinical toxicological studies or short-term trials powered for efficacy and participants in RCT may be dissimilar to individual patients seen in clinical practice. Minority groups, older individuals and those at risk of adverse events are often deliberately excluded from RCT. For example, it has been estimated that only 5% of patients typically seen in practice would be eligible to participate in a bDMARD RCT in one study.²⁰ A history of malignancy has also been an exclusion criterion for most of the bDMARD trials carried out to date. Furthermore, once marketed, it is likely that new drugs will be used in combination with other therapies, which may lead to unexpected interactions.

Post-marketing surveillance in Australia

Australia has a spontaneous reporting system that relies on voluntary reporting of suspected reactions to new drugs to the Australian Adverse Drug Reaction Advisory Committee (ADRAC).²¹ In December 2006, the Australian Adverse Drug Reactions Bulletin, noted that, based on Medicare Australia statistics, 57 846 prescriptions for the three TNF- α inhibitors combined had been issued for the treatment of RA since 2000.²² ADRAC received 319 reports of adverse events involving TNF- α inhibitors over that time period. These included 23 reports of pneumonia/lower respiratory tract infections, 10 reports of sepsis and 4 reports of tuberculosis. Other serious adverse events reported included 3 reports of malignant melanoma, 5 reports of lymphoma, 22 reports of lupus or lupus-like syndrome and 9 reports of anaphylaxis.

However, spontaneous reporting systems may considerably underestimate the incidence of adverse events as only a small proportion of suspected reactions are ever reported and information is often incomplete.²³ Although this method may provide rapid information and is effective for rare or dramatic events, it lacks a comparison group and

without reliable exposure (usage) data it is difficult to calculate the incidence of adverse reactions. Furthermore, it is unable to identify specific groups of patients who are at particular risk and establish causation and it may be incapable of detecting particular adverse effects, that is, if there is a long delay between exposure and clinical manifestation, when the drug causes an event that might be expected as part of the natural history of the disease and when adverse events already have a high prevalence in the community.

Prescriber-led patient registries or longitudinal observational studies

To overcome the limitations found with RCT and current post-marketing surveillance methods, longitudinal observational studies provide an alternative means of gathering information. Generally, these studies are implemented in the form of a health registry, where cohorts of patients are treated with routine care and are followed longitudinally without imposing inclusion or exclusion criteria.²⁴ 'Real-life' responses to therapies are systematically collected allowing questions surrounding quality of life, health-care utilization, adverse events and effectiveness of monotherapy, polytherapy and therapy switching to be addressed. Information contained in such databases may complement or be more useful than information collected by government pharmacovigilance agencies. For example, the Danish rheumatology registry detected 20 times as many adverse events as the Danish Medicines Agency in patients receiving bDMARDs, where infections and hypersensitivity reactions were the most commonly reported outcomes.²⁵

Prescriber/investigator-led patient registries have significant advantages: prescribers are clinical experts who have a vested interest in ensuring that the drugs they prescribe are safe and effective and it is likely that any findings will be rapidly disseminated and applied in clinical practice. For example, since its inception in 1999, the Australian Orthopaedic Association's National Joint Replacement Registry has quickly become the authority for information on joint-replacement surgery in Australia.²⁶ It has detected signifi-

cant variation in the practice of joint-replacement surgery within Australia and as compared with other countries and it has also identified specific prostheses or prosthetic combinations with high early failure rates.

Access to subsidized bDMARDs in Australia

Table 1 details the indications and timing of listing of bDMARDs on the Australian Pharmaceutical Benefits Scheme (PBS). Currently, strict criteria are in place for patients to access subsidized bDMARDs. This is reflected in a recent report, which indicated that less than one-quarter of the expected number of patients with RA were treated with etanercept in the year following its inclusion on the PBS.¹⁹ The more stringent criteria may mean that Australian patients are likely to have more severe disease and have been exposed to a greater number of DMARDs compared with patients in other countries.

Database overview

The specific aims of ARAD are to

- Determine the short and long-term effectiveness and safety of bDMARDs prescribed for RA and other inflammatory arthritis including psoriatic arthritis, ankylosing spondylitis and juvenile chronic arthritis, as measured by mortality/survival, function and disability, quality of life, incidence of all adverse events, treatment side-effects and reasons for stopping or changing therapy
- Determine the relative contributions of disease factors and other treatments in any risk and/or benefit observed
- Determine the economic impact of bDMARD therapy in terms of health-care and other resource utilization
- Provide confidential biannual reports of individual patient outcomes to their treating rheumatologists together with de-identified summary data
- Evaluate the tight restrictions for prescription of bDMARDs in Australia to determine whether proposed cost-effectiveness is being met and whether right target groups receive the therapy

Table 1 Indications and dates of listing of bDMARDs on the Australian Pharmaceutical Benefits Scheme (data taken from Medicare Australia <http://www.medicareaustralia.gov.au>)

Disease	Etanercept (Enbrel) [†]	Infliximab (Remicade) [‡]	Adalimumab (Humira) [§]	Anakinra (Kineret) [¶]
Severe and active rheumatoid arthritis	1 August 2003	1 February 2004	1 May 2004	1 December 2004
Severe and active juvenile chronic arthritis	1 July 2003	—	—	—
Severe and unresponsive ankylosing spondylitis	1 April 2005	1 August 2004	—	—
Severe and active psoriatic arthritis	1 August 2006	1 August 2006	1 August 2006	—

[†]Wyeth Australia, Baulkham Hills, Australia; [‡]Schering-Plough, Baulkham Hills, Australia; [§]Abbot Australia, Bottany, Australia; [¶]Amgen Australia, North Ryde, Australia. bDMARDs, biological disease-modifying anti-rheumatic drugs, —, not available for this indication on the Australian Pharmaceutical Benefits Scheme.

- Compare Australian data with overseas registries to detect country-specific differences
- Link data with overseas registries to get more accurate estimates of rare events and
- Establish a valuable ongoing data resource for answering important clinical questions that may arise in the future

A pilot study of 186 patients with RA in Victoria and New South Wales in 2001 funded by an educational grant from Aventis confirmed the feasibility of a national database. Next, we sought funding from all pharmaceutical companies involved with bDMARDs in the form of unconditional educational grants to the ARA in a deliberate attempt to encourage an all-inclusive collaborative activity. Regular meetings were conducted between the ARAD management committee and the sponsors collectively. A lobbying process was required with the national council and executive members of the ARA to establish a governance document that addressed members' concerns related to purpose, privacy, funding and data access issues. ARAD was subsequently endorsed by the ARA in November 2004.

ARAD governance

The ARA owns ARAD and controls access to, and release of, the data contained within it. The management of the database is the responsibility of the ARAD Management Committee who reports directly to the ARA executive. The ARAD Scientific Advisory Committee (SAC), which also reports to the ARA executive, is responsible for advising on policy and access to the data. Research proposals, which have ethics approval, may be submitted to the ARAD SAC for review. Further information about data access is available on the National Health and Medical Research Council Enabling Grant Facilities website (<http://nhmrc.gov.au/funding/types/granttype/access.htm>) and the ARA website (<http://www.rheumatology.org.au>). The day-to-day management of the database is the responsibility of the Project Coordinator, three State Research Officers who are responsible for different states and a data management centre team comprising a Database Architect, Data Manager and Research Assistant. These appointees work in close association with the Management Committee who meet regularly through teleconferencing, and cross-geography communication is facilitated by a Web-based project site allowing project messages and files to be uploaded. The ARA and Monash University administer the funds and an audited account is presented to the Executive monthly and to the full membership annually.

Recruitment, consent and confidentiality

The process of patient recruitment is shown in Figure 1. All patients prescribed bDMARDs in Australia are invited to

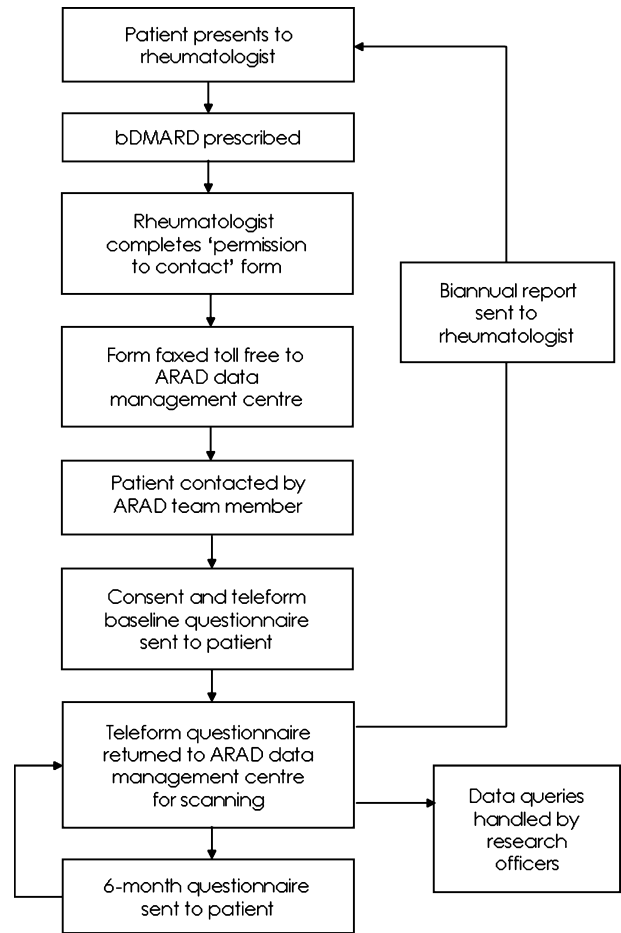


Figure 1 Flowchart of participant recruitment process into Australian Rheumatology Association Database (ARAD). bDMARD, biological disease-modifying anti-rheumatic drug.

participate in ARAD by their treating rheumatologist who describes the purpose of the database. A 'Permission to Contact' form, available from the ARA website (<http://www.rheumatology.org.au/rheumatologists/aradatabase.htm>), is then completed and faxed toll-free to the ARAD Data Management Centre. Patients are then contacted by the relevant State Research Officer who provides a more detailed explanation of the database and the patient is sent plain language and consent forms, and the baseline questionnaire. Patient consent is also obtained to access their Medicare and National/State Health Registry data. Follow-up questionnaires are mailed every 6 months. The next phase of patient recruitment will entail recruitment of controls: consecutive patients with inflammatory arthritis not taking a bDMARD.

Ethical approval for ARAD has been obtained from the Human Research Ethics Committees of Cabrini Hospital, Monash University, the Royal Children's Hospital Melbourne, South Eastern Sydney and Illawarra Area Health

Table 2 ARAD rheumatoid arthritis data collection

Rheumatologist data	Patient data	Record linkage data
Rheumatologist ID code	Demography	Medicare Australia
Diagnosis	History of arthritis	National Death Index
bDMARD prescribed	Medical history (illness, infection, cancer, symptoms)	National Cancer Statistics Clearing House
Baseline ESR	Smoking and alcohol consumption history	State and Territory Cancer Registries
Baseline CRP	Medication history	
Baseline joint count	Reasons for ceasing medication for arthritis	
Chest X-ray result	Adverse events	
Mantoux test result	Global evaluation of disease activity	
	Health Assessment Questionnaire	
	Assessment of Quality of Life	
	Short Form-36 Health Survey	
	European Quality of Life Survey	

ARAD, Australian Rheumatology Association Database; bDMARDs, biological disease-modifying anti-rheumatic drugs; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Service, Northern Sydney Health, and the Government Department of Veterans' Affairs. The database complies with the minimum guidelines for health registries for statistical and research purposes.²⁷ No patient or rheumatologist is identified in the reports and publications produced by the database.

Data collection and entry

Data collection meets the Outcome Measures in Rheumatology IV preliminary core set of domains for longitudinal observational studies in rheumatology.^{28,29} Table 2 outlines the data collected from the rheumatologist at baseline using the 'Permission to Contact' form, longitudinal data collected from the patient and record linkage data obtainable from national health bodies. Information is currently collected by means of a paper-based system using teleforms that are scanned into the database. Skilled data entry personnel check the data and correct errors. Data queries

that require patient contact are handled by the State Research Officers.

Data validation and accuracy

To ensure the success of the registry, the process of quality control and data validation undergoes continued development and refinement. We are in the process of assessing the concordance of patient responses concerning history of malignancy and adverse events to arthritis medications with the rheumatologist record in a random sample of participants. We will also determine concordance through record linkage with the State cancer registries through the National Cancer Statistics Clearing House. Other processes to ensure database quality include (i) development of a tracking log for rheumatologists to minimize selection bias by ensuring that all patients of participating rheumatologists starting bDMARDs are invited to participate in ARAD, (ii) ongoing update of a standard operating procedure

Table 3 Number of ARAD rheumatoid arthritis participants receiving a bDMARD by drug and State as of 1 August 2006 compared with number of rheumatoid arthritis patients approved for PBS-subsidized bDMARDs by drug and State 1 March 2006 to 31 August 2006[†] and number of rheumatologists participating in ARAD compared with number of fully registered ARA members by State[‡]

State/Territory	Etanercept ARAD (PBS)	Adalimumab ARAD (PBS)	Infliximab ARAD (PBS)	Anakinra ARAD (PBS)	No. rheumatologists in ARAD (no. fully registered ARA members)
NSW	153 (713)	79 (608)	8 (51)	3 (17)	45 (90)
Vic.	35 (357)	32 (496)	6 (65)	0 (8)	21 (67)
Qld	49 (215)	29 (341)	5 (46)	0 (11)	13 (33)
SA	50 (200)	23 (192)	7 (19)	2 (5)	15 (27)
WA	43 (338)	8 (275)	2 (113)	0 (4)	4 (24)
Tas.	9 (83)	16 (103)	0 (2)	0 (0)	5 (5)
ACT	3 (68)	0 (53)	0 (4)	0 (1)	1 (4)
NT	0 (7)	1 (4)	0 (0)	0 (0)	1 (2)
Total	342 (1981)	188 (2072)	28 (300)	5 (46)	105 (252)

[†]Data taken from Medicare Australia (PBS and Specialized Drugs Branch). [‡]Data taken from ARA. ARA, Australian Rheumatology Association; ARAD, Australian Rheumatology Association Database; bDMARDs, biological disease-modifying anti-rheumatic drugs; PBS, Pharmaceutical Benefits Scheme.

Table 4 Patient and disease characteristics of ARAD participants (*n* = 563), bDMARDs and concurrent DMARDs and years of use at 1 August 2006

DMARD use	<i>n</i> (%)	Mean (SD) years of intake
<i>bDMARDs</i>		
Etanercept	342 (60.7)	2.1 (1.1)
Adalimumab	188 (33.4)	1.4 (1.3)
Infliximab	28 (5.0)	2.1 (1.2)
Anakinra	5 (0.9)	2.4 (3.2)
<i>Concurrent DMARDs</i>		
Intramuscular methotrexate	94 (16.7)	6.1 (4.4)
Oral methotrexate	264 (49.6)	6.9 (4.9)
Plaquenil	104 (18.5)	5.9 (5.5)
Salazopyrin	77 (13.7)	7.2 (5.3)
Leflunomide	147 (26.1)	3.9 (2.3)
Azathioprine	11 (2.0)	5.5 (3.5)
Cyclosporine	16 (2.8)	4.9 (3.0)
Intramuscular gold	6 (1.1)	9.4 (6.3)
d-penicillamine	6 (1.1)	13.5 (10.4)
Prednisolone/prednisone	408 (72.5)	9.3 (7.1)
Other medication for arthritis	37 (6.6)	7.7 (7.0)

ARAD, Australian Rheumatology Association Database; bDMARDs, biological disease-modifying anti-rheumatic drugs; SD, standard deviation.

manual to reduce the volume of data queries (iii) ongoing update of database programmes to identify any contradictory information provided by patients and (iv) develop-

ment of a spontaneous reporting scheme for rheumatologists to report adverse events. Information about adverse events will also be forwarded to ADRAC.

Early results

According to the PBS and Specialized Drugs Branch of Medicare Australia, 4399 patients with RA were approved for PBS-subsidized bDMARDs from 1 January 2006 to 31 August 2006 (patients with more than one application in this time frame were included only once) (Table 3). As of 1 August 2006, 563 RA patients prescribed a bDMARD were enrolled in ARAD (12.8% of those approved for PBS-subsidized bDMARD). Although only a small proportion of RA patients commencing bDMARDs are currently enrolled in ARAD, recruitment is increasing and 105 committed rheumatologists, or 41.7% of registered ARA members in 2006, were participating (Table 3). As of April 2007, this has increased to 144 members (55% of ARA members in 2007). We believe this reflects a valid, 'real-world' community-based reference database as almost all RA patients commencing a bDMARD in these practices have been invited to participate and all control patients not currently prescribed a bDMARD will be drawn from the same practices. Therefore selection bias is unlikely to be a significant problem.

Demographics, disease severity and medication use among the cohort are detailed in Table 4 and quality of life as assessed by the Short Form-36 and Assessment of Quality of Life and arthritis-specific disability as assessed by the Health Assessment Questionnaire (HAQ) at

Table 5 Disability and quality of life of ARAD participants measured by the HAQ, AQoL and SF-36 at baseline, 6 and 12 months from enrolment in ARAD, and comparative Australian normative data for AQoL (women 50–59 years) and SF-36 (women 55–64 years),^{30,31} and Finnish normative data for HAQ (women 55–64 years)³²

Disability or quality-of-life index	Baseline Mean (SD)	6 months Mean (SD)	12 months Mean (SD)	Normative data Mean (SD)
HAQ [†]	1.6 (0.7) (<i>n</i> = 552)	1.2 (0.7) (<i>n</i> = 418)	1.2 (0.7) (<i>n</i> = 360)	0.2
AQoL [‡]	0.4 (0.2) (<i>n</i> = 494)	0.5 (0.3) (<i>n</i> = 69)	0.5 (0.2) (<i>n</i> = 54)	0.8 (0.2)
SF-36 [§]	(<i>n</i> = 477)	(<i>n</i> = 382)	(<i>n</i> = 334)	
Physical functioning	31.6 (23.6)	40.7 (25.7)	40.9 (25.8)	84.4 (18.9)
Role limitation due to physical problems	19.1 (32.7)	38.3 (40.6)	39.8 (42.2)	78.9 (34.4)
Role limitation due to emotional problems	46.5 (44.8)	65.8 (42.4)	65.2 (42.9)	88.4 (27.0)
Social functioning	46.1 (24.6)	59.5 (23.2)	59.1 (24.6)	87.0 (22.4)
Mental health	63.2 (20.8)	71.1 (19.7)	71.7 (19.5)	80.5 (18.0)
Vitality	33.0 (22.6)	45.3 (23.5)	44.4 (22.8)	64.6 (22.2)
Bodily pain	35.5 (22.7)	51.2 (22.9)	52.0 (23.0)	71.5 (27.0)
General health perception	37.6 (22.0)	44.5 (22.2)	43.7 (22.4)	71.2 (22.3)
Change in health	44.4 (31.7)	69.9 (28.5)	66.9 (27.7)	n/a

[†]HAQ has a range of scores 0–3: lower score indicates less disability; [‡]AQoL has a range of scores 0–1: higher score indicates better quality of life; [§]SF-36 has subscales scaled from 0 to 100 where a higher score indicates better health. AQoL, Assessment of Quality of Life Questionnaire; ARAD, Australian Rheumatology Association Database; HAQ, Health Assessment Questionnaire; n/a, data not available; SD, standard deviation; SF-36, Short Form-36 Questionnaire.

Table 6 National bDMARD registries: start date, number of participants in the registry, population source, diseases, criteria for inclusion, timing of data collection and data collected

Registry	Start date	No. participants (date of audit)	Population source	Diseases	Medication criteria for inclusion	Timing of data collection	Data collected
Consortium of Rheumatology Researchers of North America (CORRONA) ³³	2002	10 710 (June 2005)	200 rheumatologists from 83 sites across the USA	RA, PsA (Also includes OA, OP)	Not specified	Baseline and then every 3 months for RA and every 6 months for other diseases	1, 2, 7, 11, 12, 13, 15, 17
British Society for Rheumatology Biologics Register (BSRBR) ³⁴	January 2001	8455 (March 2005)	All rheumatologists	RA	bDMARD therapy	Baseline then every 6 months	1, 2, 4, 5, 6, 7, 11, 12, 14, 15
Spanish Registry for adverse events of biological therapies in Rheumatic Diseases (BIOBADASER) ^{35,36}	February 2000	4102 (April 2004)	All hospital and community rheumatology units	RA, PsA, AS, Still's, JCA	bDMARD therapy	Baseline then 6 monthly	2, 6, 7, 11, 12, 15
German Collaborative Arthritis Centres (RABBIT) ³⁷	1993	26 445 (2001)	24 arthritis centres	Inflammatory arthritis	bDMARD and DMARD therapy	Annually	1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18
Anti-Rheumatic Therapies in Sweden (ARTIS) ²⁴	1999	4160 (2003)	All rheumatologists	Inflammatory arthritis	bDMARD therapy	Baseline, 3 months, 6 months and then annually	1, 2, 3, 5, 7, 11, 12, 13
Danish Database for Biological Therapies (DANBIO) ³⁸	October 2000	3056 (June 2005)	All rheumatology departments in Denmark	RA, AS, PsA	bDMARD therapy	Baseline and each medical visit	1, 2, 3, 7, 11, 12, 13
National Register of Biological Treatment in Finland (ROB-FIN) ³⁹	March 2000	1440 (March 2005)	Voluntary rheumatology practices	RA, AS, JCA	bDMARD therapy	Baseline, 1.5, 3, 6 months, then 6 monthly	1, 2, 3, 7, 11, 12, 13
Norway Disease Modifying Anti-Rheumatic Drugs Register (NOR-DMARD) ⁴⁰	December 2000	4683 (2005)	5 rheumatology departments in Norway	RA, AS, PsA, JCA	bDMARD and DMARD therapy	Baseline, 3, 6, 12 months then annually	1, 2, 3, 4, 5, 7, 10, 11, 12, 13, 18
Research on TNF- α antagonists and opportunistic infections (RATIO) ⁴¹	February 2004	Not reported	486 hospital departments in France where bDMARDs are prescribed	Any disease for which a bDMARD (TNF- α antagonist) is prescribed	Instances where patients develop an opportunistic infection, severe bacterial infection or lymphoma	Baseline (presentation of event) with 3 year follow-up	2, 7, 11, 12
POLIDAS (Dutch Registry) ⁴²	1997	230 (September 2000)	Department of Rheumatology, RA University Medical Centre, Nijmegen	RA, AS, PsA, JCA	bDMARD therapy	Not reported	2, 3, 7, 11, 12, 13, 16
Australian Rheumatology Association Database (ARAD)	2003	1806 (April 2007)	Voluntary rheumatology practices	RA, AS, PsA, JCA	Commencement of bDMARD; controls not treated with bDMARDs	Baseline, then 6 monthly	1–18

Data collection Keys: 1. quality-of-life instruments, 2. adverse events, 3. VAS for pain/disease activity, 4. smoking history, 5. occupational history, 6. new illness diagnoses, 7. drug history and therapy changes with reason for change, 8. health insurance, 9. surgical history, 10. number of general practitioner visits, 11. demographics, 12. disease characteristics, 13. markers of disease activity, 14. extra-articular features, 15. comorbidities, 16. duration of symptoms and/or diagnosis, 17. hospitalization history and treatments, 18. absenteeism from work, AS, ankylosing spondylitis; bDMARDs, biological disease-modifying anti-rheumatic drugs; JCA, juvenile chronic arthritis; OA, osteoarthritis; OP, osteoporosis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

baseline, 6-month and 12-month intervals is outlined in Table 5. At baseline, RA patients commencing bDMARDs were significantly more disabled and had significantly lower quality of life in comparison to population norms.^{30–32} They had improved substantially within 6 months of starting bDMARD treatment and this improvement was sustained at 12 months.

Comparability to other registries

Unlike other national registries, ARAD data are derived predominantly from patient questionnaire and include a broader array of domains (Table 6). To address ARA members' concerns regarding the administrative burden, rheumatologists provide a minimum of information at baseline only. They are *not* required to regularly provide information regarding disease activity or changes in therapy. This is in contrast to other registries, such as the British Society of Rheumatology Biologics Register, where participation is mandatory and the administrative burden imposed on rheumatologists is significant.⁴³

Although the ARAD cohort has similar demographic characteristics to other national cohorts, its mean disease duration is longer, most probably reflecting the strict PBS requirements for subsidized treatment in Australia.^{25,33,39–42,44,45} A greater proportion of Australian patients has received etanercept most probably reflecting the fact that this was the first bDMARD to be listed on the PBS. Despite the longer disease duration, disability, as measured by the HAQ, is similar to patients in other registries.^{25,45–48}

Discussion

In a short period ARAD has already achieved some very important outcomes. Sufficient data are now available in ARAD to examine multiple domains of patient responses to bDMARDs, including quality of life, health-care utilization, incidence of adverse events and the effects of therapy switching. Recruitment of a control group of patients with inflammatory arthritis who are not taking bDMARDs is under way and will allow comparisons to be made. An invitation to recruit control patients has recently been extended to all participating rheumatologists to encourage recruitment of a suitable control group.

We have shown that it is possible to develop a voluntary national registry of patients with arthritis taking bDMARDs in Australia. This has been achieved by obtaining buy-in from pharmaceutical companies with an interest in bDMARDs, endorsement of the professional national body (ARA) and the effective cooperation of a large proportion of rheumatologists in Australia and, most importantly, their patients. The ARAD SAC has an important role in

encouraging colleagues in their State or rheumatology subspecialty area to participate in ARAD. This is being achieved by leading by example and providing updates on ARAD at State meetings whenever appropriate.

ARAD will be a precious Australian resource, providing valid and reliable longitudinal clinical data of persons with arthritis in Australia. Evidence-based information about long-term relevant outcomes, such as efficacy, safety and cost-effectiveness, is essential for clinicians, consumers, policy-makers, drug development companies and approval agencies to enable better care and improved outcomes. This facility will significantly underpin and enhance clinical research into arthritis in Australia. The approximation of 'real-world' conditions requires the generation of a valid reference database, sampled from the community, maintained longitudinally and free from the various biases that threaten internal validity and generalizability of the results.

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