Health-related quality of life and continuation rate on first-line anti-tumour necrosis factor therapy among rheumatoid arthritis patients from the Australian Rheumatology Association Database

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Abstract

Objectives. To describe changes in health-related quality of life (HRQoL) up to 60 months after commencing anti-TNF therapy for RA patients enrolled in the Australian Rheumatology Association Database (ARAD), and to determine the continuation rate and predictors of discontinuation of first-line anti-TNF therapy.

Methods. Responses to the HAQ, Assessment of Quality of Life, Medical Outcomes Study Short Form-36 (SF-36) and European Quality of Life-5 Dimensions (EQ-5D) were extracted from ARAD for patients commencing anti-TNF therapy and analysed in 6-monthly intervals from the start date. Predictors of discontinuation of therapy were assessed using Cox regression.

Results. Since September 2001, 2601 RA patients have enrolled in ARAD; 1801 have used anti-TNF therapy. Before starting the therapy, all HRQoL scores were below the population norms, but showed improvements in the first 6 months. From 12 to 60 months, HRQoL remained stable but below population means. Data to 60 months were available for 106 patients; 47% were still on first-line therapy at 5 years, all were using concurrent DMARDs and 55% were using concurrent prednisolone. Predictors of discontinuation of therapy were poorer HRQoL scores, a more recent therapy start date, concurrent prednisolone use and self-reported severe infection. Older patients and those with longer symptom duration were more likely to remain on therapy.

Conclusions. In routine practice, HRQoL scores improve rapidly within 6 months of starting anti-TNFs and then remain stable for up to 60 months. Almost half remain on first-line therapy.

Key words: Health-related quality of life, Biologic disease-modifying anti-rheumatic drugs, Anti-tumour necrosis factor drugs, Rheumatoid arthritis, Registry.

Introduction

RA is a chronic autoimmune disease characterized by inflammation of articular synovium that results in joint destruction [1]. It causes functional impairment and activity limitation and is associated with significant reductions in health-related quality of life (HRQoL) [2, 3]. The primary aim of treatment is to control chronic inflammation and joint damage by slowing disease activity. Traditionally, non-biologic DMARDs have been the mainstay of treatment with MTX, alone or in combination with other DMARDs, the most widely used agent [4].

More recently, biological DMARDs (bDMARDs) such as the anti-TNF agents, etanercept, infliximab and...
First-line anti-TNF therapy for RA patients from ARAD

adalimumab; the IL-1 receptor agonist, anakinra; and the B- and T-cell inhibitors, rituximab and abatacept, have revolutionized the treatment of these diseases. These drugs act rapidly to reduce inflammation and improve the clinical signs and symptoms of RA for most patients [5], but between 20 and 40% fail to respond, lose response over time or experience adverse effects [6].

In Australia, drugs listed on the Pharmaceutical Benefits Scheme (PBS) are subsidized by the Australian Government and provided to patients at a lower cost. Since there are strict requirements relating to disease status, severity and DMARD response that must be met before bDMARDs can be prescribed [7], Australian patients are likely to have a higher prevalence of comorbidities and poorer HRQoL than patients elsewhere [7].

The Australian Rheumatology Association Database (ARAD) is a voluntary national registry established in 2001 to collect longitudinal health information, including quality of life measures, from Australian patients with inflammatory arthritis. Details of the design, structure, governance and content of ARAD have been published previously [8]. One of the primary aims of ARAD is to determine the long-term benefits and safety of new treatments, in particular the bDMARDs. Participants are referred by their treating rheumatologist or they can self-refer, and ~75% of Australian rheumatologists contribute patients to the registry. Ethical approval for ARAD has been obtained from 17 committees and organizations across Australia (Appendix 1). Participants provide written informed consent to participate in the registry and to be contacted by the ARAD investigators.

Clinical trials have demonstrated improvements in physical function and quality of life for patients using anti-TNF therapies, particularly in the short term [9-13] and up to 5 years from starting treatment [3, 14-16]. Improvements in HRQoL for up to 12 months have also been reported for patients from population-based registries [17-19], but there is little information about the effects of long-term therapy with TNF inhibitors on HRQoL in a community setting.

The aims of the study were to describe changes in the HAQ, Medical Outcomes Study Short Form-36 (SF-36), the Assessment of Quality of Life (AQoL) and the European Quality of Life-5 Dimensions (EQ-5D) up to 60 months for RA patients enrolled in ARAD and on first-line anti-TNF therapy, and to determine the continuation rate and predictors of discontinuation for first-line anti-TNF therapy.

Methods

Questionnaire data

Patients generally enrol in ARAD when they are commencing their first-line bDMARD therapy. Due to the time taken for the consenting and enrolment procedures, some patients have commenced therapy before they complete their first questionnaire. The data collected in the first questionnaire include type of arthritis diagnosed, sex, date of birth, year when arthritis symptoms first appeared, year of diagnosis with arthritis, previous and current use of medication and HRQoL data measured by the HAQ, the AQoL, the EQ-5D and the SF-36 questionnaires. The treating rheumatologist provides ARAD with the ESR, CRP and active joint count that the PBS requires for authorization to prescribe bDMARD therapy. The PBS definition of an active joint count is an active (swollen and tender) joint count of at least 20 or, active joints from at least 4 of elbow, wrist, knee, ankle, shoulder or hip.

Patients complete questionnaires at 6-month intervals. These include the HRQoL questionnaires, information about any infections or other illnesses they have had since their previous questionnaire, and medication information including the dates that medications were started, stopped or recommenced since the last questionnaire. Self-reported infection is graded as mild, moderate or severe, according to OMERACT guidelines [20]. An infection is regarded as severe if the patient regards their symptoms as severe; caused a major change in activities; required a visit to a doctor; or was completely relieved by prescription medication; or resulted in temporary or permanent cessation of bDMARD treatment [20].

Outcomes

All patients in ARAD with a diagnosis of RA who had ever used anti-TNF therapy were eligible for inclusion in the study. Demographic data; responses to the HAQ, AQL, EQ-5D and SF-36 questionnaires; the date the questionnaire was completed; and the dates etanercept, infliximab and adalimumab were started, stopped and recommenced were extracted from the database for 17,176 patients enrolled in ARAD before 11 June 2009. Etanercept was the first TNF inhibitor listed on the PBS for RA (August 2003).

The HAQ is a well-validated 20-item functional assessment measure concerning eight areas of daily life [21]. The HAQ disability score ranges from 0 to 3 with higher scores representing greater disability. The minimum clinically important difference (MCID) for the HAQ in RA has been reported to be 0.22 [22].

The SF-36 is a widely used self-administered 36-item generic indicator of health status that consists of eight subscales representing eight dimensions of quality of life. Each of the eight subscales is transformed to a score ranging from 0 to 100 with higher scores representing better health and functioning. The scores can also be summarized into a physical component summary (PCS) and a mental component summary (MCS) score. Population norms have been published for Australia [23]. The MCIDs for the SF-36 scales depend on the condition under study and have been quoted as 4.4 for the PCS and 3.1 for the MCS for RA patients [24].

The AQoL is a validated multi-attribute HRQoL and utility instrument consisting of 15 items and five scales [25]. The scale scores can be converted into a utility index where 0 represents death and 1 represents perfect health; negative scores indicate a state worse than death. Australian population norms for the AQoL have been published and the MCID is 0.06 in the general population [26], but has not been determined for RA patients.
The EQ-5D is a standard general quality of life instrument encompassing five domains. The descriptive profiles from the domains can be combined to give a utility score, with the best imaginable health state representing someone who reports the highest level of functioning in each domain [27]. A minimal important difference for RA patients has been reported to be 0.13 [28].

Statistical analysis

Only patients starting first-line anti-TNF therapy have been included in this analysis. Baseline summary data were obtained from the questionnaire completed in the 6 months before starting first-line anti-TNF therapy where these were available. Age at starting first-line anti-TNF therapy was calculated from date of birth and the date the patient commenced therapy. The cumulative time, in days, spent on the initial TNF inhibitor was determined for each drug separately from the date first started to the date the drug was first stopped and summed to give an overall time on the drug. The cumulative time on first therapy was split at 6-monthly intervals beginning from Day 0. The time on anti-TNF therapy was censored at 60 months (5 years) as there were too few observations past these points to draw meaningful conclusions.

HAQ, SF-36 PCS, SF-36 MCS, AQoL and EQ-5D scores were derived using standard algorithms. Differences between the mean HRQoL scores and population values were assessed using t-tests. The influence on HRQoL measures of age, sex, concurrent DMARD and prednisolone use, years since first symptoms, calendar year of starting anti-TNF therapy and time since starting therapy were assessed using multivariable linear regression modelling. Age and sex were included in all models but other terms were added using stepwise selection and included only if they were significant at the 5% level. A conservative 5% significance level was used to ensure that robust models were obtained. Positive (negative) coefficients indicate higher (lower) scores for a variable.

Cox regression models were used to evaluate predictors of dis/continuation on first-line anti-TNF therapy and HRQoL scores, age, sex, concurrent DMARD and prednisolone use, years since first symptoms, self-report of a severe infection and calendar year of starting bDMARDs. HRQoL scores, self-report of a severe infection and concurrent DMARD use were included as time-varying covariates. Age and sex were included in all models but other terms were added using stepwise selection and included only if they were significant at the 5% level. Hazard ratios (HRs) >1 indicate a greater likelihood of discontinuing therapy and HRs <1 indicate a lower likelihood of discontinuing therapy. All analyses were performed with Stata 10 (College Station, TX, USA). Formal power calculations were not performed for this observational study, but a total of 703 patients with 535 discontinuing anti-TNF therapy would be sufficient to show a HR of >1.3 for dichotomous explanatory variables.

Results

Till 11 June 2009, there were 2601 participants in the ARAD database with a diagnosis of RA. The mean age at diagnosis was 44.1 years (s.d. 15.0 years) and 1801 had used first-line anti-TNF therapy. Etanercept was first-line therapy for 1018 (56.5%) participants, adalimumab for 643 (35.7%) and infliximab for 140 (7.8%).

The demographic characteristics of ARAD participants at the time of starting first-line anti-TNF therapy are shown in Table 1. Over 98% of participants reported concurrent use of DMARDs at that time. The most commonly used DMARD was MTX, in either oral or injectable form, taken by 71%. Seventy-five per cent reported concurrent prednisolone use.

The HRQoL scores, in 6-monthly intervals beginning before starting anti-TNF therapy, are shown in Table 2. At baseline, the SF-36 PCS, SF-36 MCS and AQoL scores were all significantly below the Australian population norms (all P’s < 0.001) [23, 26]. All HRQoL measures showed significant improvement from baseline levels within 6 months of starting therapy and the improvements over the first 6 months were greater than the reported MCID; the change in mean scores (95% CI) was −0.36 (−0.43, −0.28) for the HAQ, 4.6 (3.5, 5.7) for the SF-36 PCS, 4.2 (2.9, 5.5) for the SF-36 MCS, 0.09 (0.07, 0.12) for the AQoL and 0.16 (0.13, 0.19) for the EQ-5D. From 12 months, the HRQoL scores remained relatively stable over the subsequent intervals and below the published population norms for the SF-36 measures and the AQoL for up to 60 months.

Results of regression models investigating factors affecting HRQoL scores at baseline are shown in Table 3. In the multivariable model, older age was associated with poorer scores for all measures except the SF-36 MCS. For example, each year increase in age was associated with an increase in HAQ score of 0.013 (95% CI 0.010, 0.017) points and a decrease in SF-36 PCS score of 0.158 (95% CI 0.109, 0.206). Females had poorer HAQ scores but better SF-36 MCS and EQ-5D scores; HAQ

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA (%), n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>1314 (73.0)</td>
</tr>
<tr>
<td><strong>Clinical parameters, mean (s.d.), n</strong></td>
<td>55.9 (12.6), 1801</td>
</tr>
<tr>
<td>Age at starting anti-TNF therapy, years</td>
<td>14.7 (11.1), 1736</td>
</tr>
<tr>
<td>Years since first symptoms</td>
<td>13.0 (10.4), 1739</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>35.6 (25.6), 1023</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>27.9 (28.9), 1013</td>
</tr>
<tr>
<td>Baseline joint count (range 0–72)</td>
<td>23.2 (11.1), 1113</td>
</tr>
<tr>
<td>No. of previous DMARDS</td>
<td>3.8 (1.4), 239</td>
</tr>
<tr>
<td>Previous prednisolone, n (%)</td>
<td>158 (74.2)</td>
</tr>
<tr>
<td>(data available for 213 participants)</td>
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</tbody>
</table>
scores were 0.25 (95% CI 0.165, 0.345) points higher for females, SF-36 MCS scores 2.308 (95% CI 0.628, 3.987) points higher and EQ-5D scores 0.041 (95% CI 0.005, 0.077) points higher. Longer duration of symptoms was associated with poorer scores for the HAQ and SF-36 PCS but not the other HRQoL measures. Each year of symptoms before starting therapy was associated with an increase in HAQ score of 0.012 (95% CI 0.009, 0.016) and a decrease in SF-36 PCS score of 0.090 (95% CI 0.036, 0.144). Those starting biologics in a later calendar year had better scores for all HRQoL measures. There was no evidence of a departure from linearity for calendar year of starting therapy. Concurrent prednisolone was associated with poorer HRQoL scores as measured by the SF-36 PCS, AQoL and EQ-5D.

Continuation rates on first-line anti-TNF therapy and concurrent DMARD use are shown for 6-monthly intervals in Table 4. Approximately three-quarters of the patients continued using at least one DMARD, most commonly MTX, in conjunction with their biologic for up to 5 years. LEF, HCQ and SSZ were the next most frequently used DMARDs and these drugs were still being used by between 10 and 15% of patients after 5 years. Around half were still using prednisolone after 5 years.

Figure 1 shows the Kaplan–Meier estimates to 60 months of the proportion of patients remaining on first-line anti-TNF therapy. The median time for remaining on first-line therapy was 57 months. Table 5 shows the results of the Cox proportional hazards regression modelling of the HRQOL scores. Poorer HRQOL scores, a more recent starting date and concurrent prednisolone use were independently associated with a greater likelihood of discontinuing first-line anti-TNF therapy, while older patients and those with longer symptom duration when starting therapy had a lower risk of discontinuation. For example, a unit increase in the HAQ score when starting therapy was associated with a 44.8% (95% CI 22.1, 71.9%) increase in the likelihood of discontinuing therapy; each year increase in age was associated with a 1.1% (95% CI 0.4, 1.8%) reduction in the likelihood of discontinuation; an increase of 1 year in the calendar year of starting therapy resulted in a 12.30% (95% CI 6.3, 18.8%) increased likelihood of discontinuing; and those reporting a severe infection or concurrent use of prednisolone had 57.6% (95% CI 13.5, 118.7%) and 52.8% (95% CI 17.9, 96.0%), respectively, greater likelihood of discontinuing first-line anti-TNF therapy. Over 60% of patients who stopped their first-line therapy switched to an alternative one.

Discussion

Before starting anti-TNF therapy, RA patients in the ARAD cohort had poorer HRQoL than the general population highlighting the negative effects this disease has on quality of life. Within 6 months of starting therapy, there were rapid, clinically important improvements in all HRQoL scores, but they remained below population norms even after 5 years of treatment. Consistent with the PBS requirement for co-prescription of MTX with infliximab,
**Table 3** Regression coefficients (95% CIs) and P-values from models of factors influencing baseline HRQoL

<table>
<thead>
<tr>
<th>Baseline models</th>
<th>HAQ</th>
<th>PCS</th>
<th>MCS</th>
<th>AQoL</th>
<th>EQ-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient (95% CI)</td>
<td>P-value</td>
<td>Regression coefficient (95% CI)</td>
<td>P-value</td>
<td>Regression coefficient (95% CI)</td>
</tr>
<tr>
<td>Current age</td>
<td>0.013 (0.010, 0.017)</td>
<td>0.0005</td>
<td>-0.158 (-0.206, -0.109)</td>
<td>0.0005</td>
<td>-0.003 (-0.004, -0.002)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.255 (0.165, 0.345)</td>
<td>0.0005</td>
<td>-0.104 (-1.173, 1.264)</td>
<td>0.881</td>
<td>2.308 (0.628, 3.987)</td>
</tr>
<tr>
<td>Years between first symptoms and starting therapy</td>
<td>0.012 (0.009, 0.016)</td>
<td>0.0005</td>
<td>-0.090 (-0.144, -0.036)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Calendar year of starting first anti-TNF drug</td>
<td>-0.058 (-0.080, -0.036)</td>
<td>0.0005</td>
<td>0.433 (0.093, 0.773)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Concurrent prednisolone</td>
<td>-3.521 (-4.767, -2.277)</td>
<td>0.0005</td>
<td></td>
<td></td>
<td>-0.034 (-0.062, -0.005)</td>
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</table>

Denominators vary according to drug.

**Table 4** Drug continuation and concomitant DMARD use in 6-monthly intervals after starting first-line anti-TNF therapy

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Number starting interval</td>
<td>1801</td>
<td>1373</td>
<td>1144</td>
<td>924</td>
<td>743</td>
<td>586</td>
<td>442</td>
<td>325</td>
<td>245</td>
<td>184</td>
</tr>
<tr>
<td>Proportion remaining on therapy (95% CI)</td>
<td>0.85 (0.83, 0.87)</td>
<td>0.79 (0.78, 0.82)</td>
<td>0.72 (0.71, 0.75)</td>
<td>0.67 (0.66, 0.71)</td>
<td>0.63 (0.61, 0.66)</td>
<td>0.59 (0.56, 0.62)</td>
<td>0.54 (0.51, 0.57)</td>
<td>0.52 (0.49, 0.55)</td>
<td>0.50 (0.48, 0.54)</td>
<td>0.47 (0.44, 0.51)</td>
</tr>
<tr>
<td>Number censored</td>
<td>170</td>
<td>135</td>
<td>130</td>
<td>123</td>
<td>109</td>
<td>109</td>
<td>96</td>
<td>67</td>
<td>56</td>
<td>68</td>
</tr>
<tr>
<td>Prednisolonea, n (%)</td>
<td>777 (70.1)</td>
<td>598 (62.7)</td>
<td>401 (61.9)</td>
<td>312 (55.3)</td>
<td>262 (55.0)</td>
<td>254 (59.5)</td>
<td>181 (57.3)</td>
<td>141 (56.0)</td>
<td>102 (57.6)</td>
<td>79 (52.0)</td>
</tr>
<tr>
<td>Any DMARDa, n (%)</td>
<td>947 (80.5)</td>
<td>703 (80.3)</td>
<td>537 (77.8)</td>
<td>460 (77.4)</td>
<td>372 (74.4)</td>
<td>341 (77.0)</td>
<td>248 (74.5)</td>
<td>196 (75.7)</td>
<td>136 (74.3)</td>
<td>115 (73.7)</td>
</tr>
<tr>
<td>1 DMARDa, n (%)</td>
<td>524 (42.7)</td>
<td>396 (45.3)</td>
<td>320 (46.4)</td>
<td>302 (50.8)</td>
<td>241 (48.2)</td>
<td>229 (51.5)</td>
<td>166 (49.8)</td>
<td>138 (53.3)</td>
<td>98 (53.6)</td>
<td>88 (56.4)</td>
</tr>
<tr>
<td>2 DMARDa, n (%)</td>
<td>322 (26.3)</td>
<td>235 (26.9)</td>
<td>170 (24.6)</td>
<td>131 (22.1)</td>
<td>104 (20.8)</td>
<td>98 (22.1)</td>
<td>71 (21.3)</td>
<td>51 (19.7)</td>
<td>31 (16.9)</td>
<td>23 (14.7)</td>
</tr>
<tr>
<td>&gt;3 DMARDa, n (%)</td>
<td>140 (11.4)</td>
<td>72 (8.2)</td>
<td>47 (6.8)</td>
<td>27 (4.9)</td>
<td>15 (3.4)</td>
<td>11 (3.3)</td>
<td>7 (2.7)</td>
<td>7 (3.8)</td>
<td>4 (2.6)</td>
<td></td>
</tr>
</tbody>
</table>

Denominators vary according to drug.
60% of patients overall continued concurrent MTX, while 75% continued to use at least one DMARD after 5 years and 55% remained on prednisolone.

In this cohort of patients with active RA who qualified for anti-TNF therapy in Australia, independent predictors of poorer HRQoL when starting therapy were older age and concurrent prednisolone use. Better baseline HRQoL scores were seen for patients with a more recent calendar year of starting biologics. After 1 year, over three-quarters remained on their first-line anti-TNF therapy and around half were still on it after 5 years.

Socio-demographic differences in quality of life in RA have been documented previously [26, 29]. Age- and sex-specific norms available for the SF-36 [23, 30], AQoL [26] and EQ-5D [31] indicate poorer SF-36 PCS [32], AQoL [26] and EQ-5D [31] scores for older people, but no real differences between males and females. Many [33–37], but not all studies [38, 39], have reported that longer disease duration is associated with poorer HRQoL. In line with the strict PBS requirements for prescription of bDMARDs in Australia, all our study population had severe, active disease unresponsive to DMARD therapy as evident from their elevated baseline ESR, CRP and active joint counts. They therefore represent a more severe subset of RA than is likely to be present in a general RA clinical cohort, and compared with an earlier clinical cohort of Australian patients with RA, they had higher HAQ and lower SF-36 PCS scores [32, 37].

Patients starting therapy in more recent years tended to have better HRQoL when starting. This is likely to reflect a first bDMARD cohort effect. When bDMARDs first became available, they offered a new line of therapy for chronic non-responders to conventional DMARDs who had limited treatment options and continuing poor HRQoL. A high proportion of those chronic non-responders and continuing poor HRQoL would have led to chronic non-responders with poorer HRQoL. There is evidence that the HRQoL benefits of anti-TNF therapy may be more evident in terms of physical improvements than mental outcomes [3, 10, 15–17, 40].

There have been documented previously [26, 29]. Age- and sex-specific norms available for the SF-36 [23, 30], AQoL [26] and EQ-5D [31] indicate poorer SF-36 PCS [32], AQoL [26] and EQ-5D [31] scores for older people, but no real differences between males and females. Many [33–37], but not all studies [38, 39], have reported that longer disease duration is associated with poorer HRQoL. In line with the strict PBS requirements for prescription of bDMARDs in Australia, all our study population had severe, active disease unresponsive to DMARD therapy as evident from their elevated baseline ESR, CRP and active joint counts. They therefore represent a more severe subset of RA than is likely to be present in a general RA clinical cohort, and compared with an earlier clinical cohort of Australian patients with RA, they had higher HAQ and lower SF-36 PCS scores [32, 37].

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<table>
<thead>
<tr>
<th>Variable</th>
<th>HAQ, HR (95% CI)</th>
<th>P-value</th>
<th>SF-36 PCS, HR (95% CI)</th>
<th>P-value</th>
<th>SF-36 MCS, HR (95% CI)</th>
<th>P-value</th>
<th>AQoL, HR (95% CI)</th>
<th>P-value</th>
<th>EQ-5D, HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRQoL measure</td>
<td>1.448 (1.221, 1.719)</td>
<td>0.005</td>
<td>0.966 (0.955, 0.978)</td>
<td>0.0005</td>
<td>0.988 (0.979, 0.998)</td>
<td>0.015</td>
<td>0.413 (0.252, 0.678)</td>
<td>0.0005</td>
<td>0.349 (0.234, 0.551)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Age at starting first bDMARD</td>
<td>0.989 (0.987, 0.996)</td>
<td>0.002</td>
<td>0.987 (0.980, 0.994)</td>
<td>0.0005</td>
<td>0.994 (0.987, 1.000)</td>
<td>0.005</td>
<td>0.902 (0.896, 0.999)</td>
<td>0.024</td>
<td>0.993 (0.986, 0.999)</td>
<td>0.037</td>
</tr>
<tr>
<td>Sex</td>
<td>1.075 (0.990, 1.283)</td>
<td>0.453</td>
<td>1.135 (0.996, 1.371)</td>
<td>0.191</td>
<td>1.170 (0.971, 1.410)</td>
<td>0.100</td>
<td>1.186 (0.984, 1.430)</td>
<td>0.073</td>
<td>1.241 (1.029, 1.497)</td>
<td>0.023</td>
</tr>
<tr>
<td>Calendar year of starting</td>
<td>1.123 (1.003, 1.188)</td>
<td>0.005</td>
<td>1.132 (1.070, 1.198)</td>
<td>0.0005</td>
<td>1.096 (1.034, 1.157)</td>
<td>0.001</td>
<td>1.113 (1.054, 1.177)</td>
<td>0.0005</td>
<td>1.123 (1.063, 1.187)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Years between first symptoms</td>
<td>0.986 (0.978, 0.994)</td>
<td>0.001</td>
<td>0.987 (0.979, 0.995)</td>
<td>0.002</td>
<td></td>
<td></td>
<td>0.990 (0.982, 0.998)</td>
<td>0.013</td>
<td>0.989 (0.981, 0.997)</td>
<td>0.006</td>
</tr>
<tr>
<td>and starting therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.241 (1.029, 1.497)</td>
<td>0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported severe infection</td>
<td>1.576 (1.135, 2.187)</td>
<td>0.007</td>
<td>1.474 (1.057, 2.056)</td>
<td>0.023</td>
<td>1.718 (1.246, 2.370)</td>
<td>0.001</td>
<td>1.604 (1.154, 2.229)</td>
<td>0.005</td>
<td>1.575 (1.135, 2.184)</td>
<td>0.007</td>
</tr>
<tr>
<td>Concurrent prednisolone</td>
<td>1.520 (1.179, 1.960)</td>
<td>0.001</td>
<td>1.405 (1.087, 1.817)</td>
<td>0.010</td>
<td>1.537 (1.193, 1.980)</td>
<td>0.001</td>
<td>1.487 (1.155, 1.914)</td>
<td>0.002</td>
<td>1.433 (1.113, 1.846)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
randomized controlled trials found the SF-36 PCS score to be more responsive to health status changes following initiation of anti-TNF therapy than the SF-36 MCS score. Some clinical trials [3, 16] have shown greater improvements in PCS scores than MCS scores for patients on TNF inhibitors compared with those on placebo. Patients on the Dutch RA Monitoring (DREAM) register [17] had poorer PCS scores than the US population norms, but normal MCS scores when starting TNF-α therapy. After 1 year, PCS and HAQ scores showed significant improvements over their levels at commencement of therapy. One study, however [15], reported improvements in both PCS and MCS scores to at least population levels after 52 weeks for patients taking adalimumab. Our results may reflect differences between community-based and clinical trial populations or the larger size of our cohort may provide sufficient power to detect the smaller clinically important differences for the SF-36 MCS score.

Our 12-month data are consistent with those of other registry studies that have assessed changes in HRQoL with commencement of anti-TNF therapy. Changes in HRQoL for patients using anti-TNF therapy and enrolled in other registries indicate improvements to 12 months in HAQ [17, 19], SF-36 PCS [17] and EQ-5D [17] scores. We demonstrated very little change in HRQoL between 12 and 60 months, but there is little long-term data available from other registries to be able to make comparisons.

Independent predictors of discontinuation on first-line anti-TNF therapy were poorer HRQoL scores, a more recent start date, concurrent prednisolone use and self-reported severe infection, while older patients and those with longer symptom duration when starting therapy were less likely to discontinue. Many patients commencing anti-TNF therapy when it first became available in Australia had failed DMARDs and were probably quite resilient at coping with their longstanding active disease. These patients may also be more reluctant to stop them if partially effective. More recent starters could commence bDMARDs after 6–12 months of DMARD therapy, before their quality of life deteriorated, and may have higher expectation of remission than those with longer standing disease. These patient expectations are not unrealistic as they reflect treating physician expectations. Compared with 10 years ago, rheumatologists now have access to a greater range of therapies available for this disease. Furthermore, rheumatologists are beginning to accept and promulgate the promise of treat-to-target strategies [41], the target being remission, as the evidence base for this paradigm shift accumulates [42].

While Heiberg et al. [18] reported that discontinuation of anti-TNF therapy was less likely for RA patients on concomitant MTX than for those on anti-TNF therapy alone, we saw no evidence of this perhaps because of the high proportion of our patients on concurrent MTX. The effect of concurrent prednisolone on continuation of therapy does not appear to have been reported previously, making it difficult to put our finding of a higher risk of discontinuing therapy for patients using concurrent prednisolone into context.

Our 1-year retention rates were slightly lower than those reported for several clinical trials that have reported retention rates of ~80% [43]. This is consistent with the reduced effectiveness of therapy that is likely to occur in routine care compared with the highly controlled setting of clinical trials. However, our 1-year retention rates on first-line anti-TNF therapy were also lower than those from the Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER) registry [44] where the median time on anti-TNFs was 768 days (25 months) and retention rates were between 81 and 87% depending on the drug. This is likely to be influenced by the need for Australian patients to meet response criteria at each new 6-monthly prescription with at least 50% reduction in active joint counts and at least 20% reduction in inflammatory markers (ESR and/or CRP) from baseline. On the other hand, considerably lower retention rates of ~65% were reported for RA patients from the Norwegian DMARD register who were on anti-TNF drugs [18].

Interestingly, our 5-year retention rate of first-line anti-TNF therapy was lower than the 72% 5-year retention rate reported for MTX in an Australian community practice before the introduction of bDMARDs in clinical practice [45]. At that time, there were no other treatment options and the continuation rate is less likely to reflect truly adequate disease control.

There are several limitations to our study. We have combined anti-TNF drugs in assessing continuation of first-line therapy due to the low numbers of patients taking infliximab and the different timing of introduction of each drug into clinical practice in Australia. It is likely that continuation rates could vary between anti-TNF drugs. A recent overview [46] using indirect comparisons of etanercept, adalimumab, infliximab, rituximab and anakinra from clinical trial data found fewer withdrawals from etanercept despite similar efficacy for all biologics except anakinra. There was significant heterogeneity between the trial populations and these populations are also likely to be different from community-based patients.

There are still areas that warrant further research. We have found that more recent cohort patients also appeared to be switching from their first-line anti-TNF therapy earlier, with 60% of those stopping taking another bDMARD. The efficacy of second-line bDMARD therapy also needs investigation to determine whether there are better long-term outcomes in a real-life setting. As more patients on second- and third-line therapy are accrued, we can address these issues. Early DMARD-based therapy, both biologic and traditional, prevents joint damage and should be instituted as soon as possible despite the failure rate of biologics due to lack of efficacy, contraindications and intolerance [47]. The incidence of malignancies in these patients on immunosuppressants also needs to be investigated and will be the subject of future analyses from the ARAD cohort.

In summary, we found that RA patients on anti-TNF therapy showed rapid and sustained clinically important improvements in HRQoL. Around half of the patients were
still on first-line therapy after 4.5 years, while more than half of the others had switched to another bDMARD. A high percentage of all patients continued to use other anti-rheumatic drugs including prednisolone, but their HRQoL remained below population norms even after 60 months of therapy. Prednisolone use was associated with worse baseline HRQoL and higher discontinuation rates. Early assessment and treatment before significant HRQoL decline has occurred should now be the goal for all RA patients.

**Rheumatology key messages**

- Patients on anti-TNF therapy showed rapid, sustained improvements in HRQoL
- HRQoL for patients on first-line anti-TNF therapy remained below population norms after 60 months.
- After 5-year follow-up, 50% of patients remained on first-line anti-TNF therapy.

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Appendix 1
List of Australian Institutional Human Research Ethics Committees

ACT Health and Community Care Human Research Ethics Committee (HREC); AIHW Australian Institute of Health and Welfare Ethics Committee; Cabrini Hospital HREC; Australian Government Department of Veterans’ Affairs HREC; Monash University Research Ethics Committee; Northern Sydney Health HREC (Hawkesbury); Cancer Institute NSW Ethics Committee; HREC of Northern Territory Department of Health and Families and Menzies School of Research; Princess Margaret Hospital Western Australia; Queensland Health Research Ethics Committee; Royal Children’s Hospital HREC, Melbourne; South Australia Department of Health HREC; South Eastern Sydney and Illawarra Area Health Service Central Network HREC – St George; St Vincent’s Hospital (Melbourne) Ltd HREC A; Tasmania Health and Medical HREC; and The Cancer Council Victoria HREC; Department of Health WA HREC.