

Outcomes with Biological Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) in Older Patients Treated for Rheumatoid Arthritis



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ABSTRACT

Background

Biological disease-modifying antirheumatic drugs (bDMARDs) are recommended for rheumatoid arthritis (RA), but older patients reportedly experience more adverse events (AEs) and show variable treatment response. The objective of this study was to evaluate AEs and effectiveness of bDMARDs in a cohort of older patients.

Methods

AE and treatment effectiveness (based on DAS28 scores) data from a prospective provincial pharmacovigilance program for the years 2006–2009 in patients 55–64, 65–74, and 75+ years of age were compared. An intention to treat analysis with chi-square and unpaired *t*-testing for significance was performed.

Results

There were a total of 333 patients (156 were aged 55–64, 125 were 65–74, 52 were 75+). Those 75+ had higher disease activity and worse functional status at baseline. Among those 75+, AEs with bDMARDs were more common and likely to lead to discontinuation of therapy, be graded as severe, and classified as infectious ($p < .05$). Remission rate among those 75+ was significantly higher than patients 65–74. Etanercept was the most commonly used drug in all age groups.

Conclusion

Patients 75+ treated with bDMARDs are at a significantly greater risk of AEs, including infectious ones. The higher remission found in the oldest age group warrants further study.

Key words: late onset rheumatoid arthritis, rheumatoid arthritis, older age, biological disease-modifying anti-rheumatic drugs, adverse events, effectiveness, safety

INTRODUCTION

Rheumatoid arthritis (RA) is common among older patients with studies showing that the cumulative risk rises in both sexes until around sixty, when the incidence is highest.⁽¹⁾ Late-onset rheumatoid arthritis (LORA), defined as onset after 60 years of age, accounts for 10–33% of all cases of the disease.^(2,3) Patients with advanced LORA are at higher risk of functional decline, falls, and cognitive impairment.⁽⁴⁾

Although treatment with biological disease-modifying antirheumatic drugs (bDMARDs) intended to achieve either remission or low disease activity (LDA) is recommended in both the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) guidelines, studies indicate that older patients experience more adverse events (AEs) with these agents.⁽⁵⁻⁷⁾ Advanced age has also been stated to predict relatively worse treatment response in some studies,⁽⁸⁾ possibly because of greater disease severity and functional limitations at the initiation of therapy, but other studies have reported equivalent outcomes to what is seen in younger patients.^(4,9,10)

The objective of our study was to examine the likelihoods of AEs and a favourable treatment response (remission or LDA) in middle-aged and older patients treated with bDMARDs. We were particularly interested in comparing the relative effectiveness and rates of AEs associated with bDMARDs in three age groups—those 75+, 65–74, and 55–64 years of age. Our hypothesis was that AEs would be more common in the oldest age group, but effectiveness (as measured by the Disease Activity Score 28 or DAS28) would be equivalent.

Methods

A retrospective cohort analysis of data on patients prospectively recruited into the Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics Cohort

(RAPPORT) was conducted on patients 55+ with RA treated with bDMARDs. This province-wide program was established in 2004 through a partnership between the Universities of Alberta and Calgary, pharmaceutical industry, Alberta Institute of Health Economics, and Alberta Blue Cross. The primary aims of the program were to enhance the education and care of patients receiving biologics for RA, and systematically capture data on the safety, effectiveness, and cost-benefit of biologics.⁽¹¹⁾ Access to bDMARD therapy during the time period of the study required the consent of the patient and attending clinician to provide data to RAPPORT collected at baseline, three months post-enrollment, and then every six months. Data from RAPPORT has been used in several prior publications where additional information can be found on it.⁽¹²⁻¹⁴⁾ The RAPPORT database, and its subsequent use for studies, received ethical approval from the Universities of Alberta and Calgary health ethics review boards. Enrolled patients had to provide their consent. This specific study received approved from the Conjoint Health Research Ethics Board (CHREB) of the University of Calgary.

Inclusion criteria for this study were: patient age 55+ at initial visit, diagnosis of RA, treatment with a bDMARD approved by Alberta Blue Cross for RA, bDMARD treatment initiated after December 31, 2006 and before August 1, 2009, and RAPPORT data available from one or more visits. These dates were selected based on advice from the data stewards to minimize missing data for the variables used in our analyses. The rate of missing data for the occurrence of AEs, baseline Health Assessment Questionnaire (HAQ) scores, baseline Disease Activity Score (DAS) 28 scores, and follow-up DAS28 scores were 0.6%, 2.7%, 5.1%, and 12.9%, respectively. There were a total of 43 people who had no recorded visits subsequent to their baseline visit. Six of them had AEs data recorded in the database, but it is not known how this information was collected or how systematically AE data were collected on the 43 with no recorded follow-up visits. These 43 patients were excluded from our analysis of AEs, but retained in our intention-to-treat (ITT) assessment of effectiveness (our definition for effectiveness required remaining on the bDMARD, and continued provision of the bDMARD was conditional on the submission of follow-up data indicating pre-specified efficacy outcomes were being met⁽¹³⁾). An observed cases (OC) evaluation of effectiveness restricted to those who returned for a follow-up assessment was also conducted. Baseline characteristics of these 43 people, including baseline HAQ score and baseline DAS scores, did not differ significantly ($p > .05$) from those who had a follow-up visit.

Baseline characteristics examined included age, sex, DAS28 score (i.e., assessment of RA activity based on examination of 28 joints and the ESR),⁽⁶⁾ and HAQ scores. The HAQ is a validated tool for the measurement of functional status and disability in RA. The total score is between 0–3.0, with increasing scores indicating worse functioning. A score of 0 means no functional impairment, while 3 indicates the person is unable to perform functional activities.⁽¹⁵⁾

AEs of particular interest with the use of bDMARDs (e.g., infections, malignancies) were ascertained by review of their electronic medical records by specially trained nurse coordinators, as well as patient self-report. Information on AEs in the database included type of reaction, severity according to OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) grading scale, presumed association to the bDMARD prescribed, countermeasures, and outcomes.⁽¹⁶⁾ According to OMERACT, a mild (Grade 1) AE is characterized by either no or transient (lasting less than one week) symptoms requiring no lifestyle modification or medication. Moderate (Grade 2) ones are characterized by symptoms that last one to two weeks that resulted in a lifestyle change and/or required a medication. Severe (Grade 3) events are marked by reversible but prolonged symptoms causing a major functional impairment, requiring prescription medication, hospitalization for less than 24 hours, and/or temporary-to-permanent study drug discontinuation. Grade 4 AEs are life-threatening ones that lead to substantial disability and/or hospitalization for more than 24 hours with permanent study drug discontinuation.⁽¹⁶⁾

For the assessment of the effectiveness of treatment, patients had to remain on therapy and show a positive response on the DAS28, which is endorsed by the American College of Rheumatology (ACR) as a validated measure of disease activity and outcome.⁽⁶⁾ A DAS28 score greater than 5.1 is regarded as high disease activity, with moderate disease activity indicated by a score ≥ 3.2 to ≤ 5.1 , low disease activity (LDA) by one of ≥ 2.6 to < 3.2 , and disease remission by a score of less than 2.6.⁽⁶⁾ We focused on whether patients achieved criteria for either remission or LDA with treatment.⁽⁶⁾

Missing data were not imputed. Descriptive statistics and comparisons are based on patients with no missing data for the specific characteristic being examined. The study cohort was grouped by age categories (75+, 65–74, 55–64) at the time of the initial visit. Descriptive statistics (means, standard deviations, percentages) were calculated for baseline characteristics. Our primary objective was to compare AEs (rate, severity, types of adverse events) and effectiveness of bDMARDs in the three age categories. As secondary objectives, we explored if sex, disease activity, baseline functional impairment, and the type of bDMARDs prescribed differed across the three age groups we examined. For the primary objectives (AEs, treatment effectiveness) we performed an intention-to-treat analysis for the three age groups with two-tailed Fischer's exact tests for categorical variables and unpaired *t*-test for continuous ones, with an alpha of 0.05 used as the cutoff for statistical significance. We did not correct for multiple comparisons. Because of relatively small numbers (especially for the 75+ age group), we did not perform regression analyses to search for other predictors of either AEs or treatment effectiveness.

Results

A total of 333 patients met entry criteria. Of this group, 52 (15.6%) were 75+ years of age, 125 (37.5%) 65–74, and 156

(46.8%) 55–64. There were 231 female (69.4%) and 102 male (30.6%) patients. Of the 333 patients, 218 (65.5%) were from Edmonton and 115 (34.5%) were from Calgary. The entire group accounted for a total of 1,131 documented visits (i.e., both baseline and follow-up) over the time frame of the study.

Baseline characteristics are shown in Table 1. There was no significant difference in sex distribution across the age categories. Baseline disease activity status based on DAS28 score prior to starting treatment with bDMARDs was significantly higher among those 75+ compared to the 55–64 group ($p = .019$), though it is noted that, at baseline, all age groups had a high disease activity status as defined by a mean DAS28 score of greater than 5.1. The 75+ group had a statistically higher level of functional impairment prior to therapy initiation based on their mean HAQ score, as compared to the 65–74 and 55–64 groups (p values = .003 and .0001, respectively). The absolute differences in mean values between those 75+ and the two younger (65–74 and 55–64) groups were 0.33 and 0.44, respectively. The Minimal Clinically Important Difference (MCID) for the HAQ is 0.22.^(17,18) Baseline functional status was not significantly different between the 65–74 and 55–64 groups ($p = .167$). The absolute difference between mean HAQ values was 0.11, less the noted MCID.

Etanercept was the most commonly used bDMARD (59.6%, 57.6%, and 48.1% of the 75+, 65–74, and 55–64 age groups, respectively, were prescribed this agent). Adalimumab and infliximab were the next most commonly used agents across all age groups. Rituximab and abatacept were used infrequently in all groups. The distribution of the types of biologic drugs used in the three age groups was not statistically different.

AE data are shown in Table 2. As previously noted, for the AE analysis, the 43 patients who did not have a follow-up visit were excluded, resulting in a total of 290 for this outcome. Of the 290, 48 were (16.6%) were 75+ years of age, 103

(35.5%) were 65–74, and 139 (47.9%) were 55–64. Patients 75+ experienced a statistically higher rate of AEs compared to those 65–74 ($p = .0259$), and a significantly higher AEs rate when compared to the two younger groups combined ($p = .0427$). Infections were the most commonly reported AEs for all ages, but the rate was significantly higher among those 75+ compared to the younger age groups. Genitourinary and pulmonary infections were the most commonly reported infections. AEs leading to drug discontinuation and those deemed as Grade 4 (i.e., life-threatening) were significantly more likely in the 75+ age group. While multiple AEs were more common among those 75+, this was not statistically significant ($p = .0524$ when the rate among those 75+ was compared to both younger groups combined). Rates of AEs did not differ significantly by sex across the three age groups ($p > .5$).

Effectiveness data is shown in Table 3. Patients 75+ were statistically more likely to achieve remission than patients 65–74 ($p = .0265$) in the ITT analysis, but the difference in proportions achieving remission was not significant in the OC assessment ($p = .0689$). Other comparisons were not statistically significant. LDA was achieved in similar proportions across the three age groups. Overall therapy effectiveness (combined remission and LDA rate) did not differ significantly by sex across the three age groups ($p > .05$).

DISCUSSION

Older patients with RA, especially those with significant comorbidities, were typically excluded from the phase III drug studies that led to the approval of bDMARDs. The available reports on LORA do not include large numbers of patients aged 75 years or greater. Decisions on their care typically are based on extrapolating evidence from younger and/or fitter populations. Treatment with bDMARDs has made a significant impact on the management of RA. However, direct

TABLE 1.
Baseline characteristics

	Age 75+ N=52	Age 65–74 N=125	Age 55–64 N=156	P value
Age (Mean, SD)	78.42 (3.11)	68.75 (2.86)	59.58 (2.74)	$p < .0001^a$
Sex – Woman (N and %)	40 (76.9%)	86 (68.8%)	105 (67.3%)	$p > .05$
DAS 28 score (Mean, SD)	6.52 (1.23)	6.23 (1.31)	6.01 (1.16)	$p < .02^b$
HAQ score (Mean, SD)	2.16 (0.53)	1.83 (0.58)	1.72 (0.57)	$p < .003^c$
Infliximab ^d (N and %)	7 (13.5%)	14 (11.2%)	26 (16.7%)	
Etanercept ^d	31 (59.6%)	72 (57.6%)	75 (48.1%)	
Adalimumab ^d	14 (26.9%)	27 (21.6%)	49 (31.4%)	
Abatacept ^d	1 (1.9%)	8 (6.4%)	8 (5.1%)	
Rituximab ^d	3/52 (5.8%)	7 (5.6%)	8 (5.1%)	

a value $< .05$ for 75+ vs. 65–74, 75+ vs. 55–64, and 65–74 vs. 55–64.

b P value $< .05$ for 75+ vs. 55–64.

c P value $< .05$ for 75+ vs. 65–74 and 75+ vs. 55–64.

d P value $> .05$ for 75+ vs. 65–74, 75+ vs. 55–64, and 65–74 vs. 55–64

TABLE 2.
Adverse events

Adverse Events (AEs) (Number, %)	Age 75+ n=48	Age 65-74 n=103	Age 55-64 n=139
Total AEs	18 (37.5%) ^{a,b}	21 (20.4%)	34 (24.5%)
Drug discontinuation	10 (20.8%) ^{a,b}	9 (8.7%)	11 (7.9%)
Drug stop/start due to AE ^c	7 (14.6%)	10 (9.7%)	16 (11.5%)
Grade 1 AEs ^d	2 (4.2%)	2 (1.9%)	1 (0.7%)
Grade 2 AEs ^e	3 (6.3%)	12 (11.7%)	15 (10.8%)
Grade 3 AEs ^f	7 (14.6%)	6 (5.9%)	14 (10.1%)
Grade 4 AEs ^g	6 (12.5%) ^{a,h,b}	1 (1.0%)	4 (2.9%)
Multiple AEs	8 (16.7%)	7 (6.8%)	11 (7.9%)
Infectious AEs	13 (27.1%) ^{a,b,h}	13 (12.6%)	18 (12.9%)

^a P value < .05 for 75+ vs. 65–74.

^b P value < .05 for 75+ vs. 65–74 and 55–64 combined. ^cTemporary drug discontinuation and restart due to an adverse event.

^d Grade 1 AE: Mild AEs characterized by either no or transient (lasting less than one week) symptoms requiring no lifestyle modification or medication.

^e Grade 2 AE: Moderate AEs characterized by symptoms that last one to two weeks that resulted in a lifestyle change and/or required a medication.

^f Grade 3 AEs: Severe AEs marked by reversible but prolonged symptoms causing a major functional impairment, requiring prescription medication/partial relief, hospitalization for less than 24 hours, and/or temporary to permanent study drug discontinuation.

^g Grade 4 AEs: Life-threatening AEs that lead to substantial disability and/or hospitalization more than 24 hours with permanent study drug discontinuation.

^h P value < .05 for 75+ vs. 55–64.

TABLE 3.

Relative treatment effectiveness (intention-to-treat analysis)

Treatment Outcome (Number, %)	Age 75+ n=52	Age 65-74 n=125	Age 55-64 n=156
Remission ^a	17 (32.7%) ^b	21 (16.8%)	40 (25.6%)
Low disease Activity (LDA) ^c	5 (9.6%)	23 (14.7%)	23 (14.7%)
Remission or LDA	22 (42.3%)	44 (35.2%)	63 (40.4%)

^a Remission defined by a DAS28 score of less than 2.6.

^b P value < .05 for 75+ vs. 65–74.

^c Low disease activity defined by DAS28 score of ≥ 2.6 to < 3.2 .

evidence of the benefits of bDMARDs in older populations is relatively scarce with inconsistent results. Their safety profile has been a major area of concern. AEs reported with bDMARDs include, but are not limited to, infusion reactions, serious infections including recurrence of tuberculosis, non-melanoma skin cancer, neurological events, gastrointestinal perforations, venous thromboembolism, and elevation of liver enzymes.⁽¹⁹⁾ There is debate about whether older patients have an equivalent or worse likelihood of benefiting from these agents. A recent systematic review and meta-analysis concluded that older patients had more safety issues, showed less of a response to biological agents than younger patients, and had worse baseline RA disease activity.⁽²⁰⁾

Our retrospective analysis showed that patients 75+ with RA in Alberta were more likely to experience AEs compared to the 65–74 group and the two younger age groups combined. These AEs were also more likely to be infectious, life threatening, and lead to discontinuing treatment. Our findings are

consistent with a number of previous reports on this topic.^(9,10,20-22) We found higher baseline RA disease activity in the 75+ group compared to the 55–64 one. This is also consistent with most previous reports,^(2,4,7,10,20) though some have reported similar baseline disease activity.^(9,23) Like Filippini *et al.*⁽⁷⁾ we found worse baseline function in older patients as shown by the higher mean HAQ score in the 75+ group. As noted, the absolute differences in mean HAQ values were greater than the MCID for this measure.

An unexpected finding in our ITT analysis was the significantly higher remission rate in those 75+ compared to those 65–74 years of age. This has not been previously reported. Older patients in general have been reported to have a comparatively worse response rate.^(4,7,9,10,20) We looked specifically at patients 75+ (old-old group) as well as those 65–74 (young-old one), which differs from previous reports, other than the study by Payet *et al.*⁽²³⁾ that reported on the 75+ and 65–74 age groups. Our finding will require confirmation, and it would be premature to suggest that this is related to the age of the patients. Other than occurring purely by chance, it might be explained by two factors: selection bias (i.e., those 75+ offered therapy may have been in particularly good general health compared to age-matched peers and patients 65–74, though this is not reflected by either our DAS 28 or HAQ data), and unmeasured confounders that influenced treatment response. As noted, we did not correct for multiple comparisons, statistical significance for the finding was lost in our OC analysis, and there was significant differences between the two when we looked at a combined remission and LDA outcome.

There is evidence that the subjective components of the DAS28 are rated lower by older patients, which may have contributed to lower values on this measure and a higher

determination of remission in the oldest age group.⁽²⁴⁾ Burmeister and colleagues in the Research in Active RA (ReAct) trial showed that male sex was associated with achieving remission or LDA.⁽²⁵⁾ We didn't find this, but were likely inadequately powered to detect it (we only had 12 men in the 75+ age group). The ReAct prospective trial also found that patients with moderate disease severity were more likely to achieve remission or mild disease activity compared with patients with more severe disease activity.⁽²⁵⁾ Shorter disease duration (less than two years), younger age, one co-morbidity, and no previous TNF inhibitor use were other predictors of remission or mild disease activity.^(25,26) We did not evaluate the influence of the other characteristics on AEs and effectiveness because either the data were not available or our sample was too small.

TNF inhibitors were the most commonly used bDMARDs in our study. They are also the most studied class of bDMARDs.^(20,27) Etanercept was the most commonly used TNF inhibitor in all age groups, followed by adalimumab and infliximab. Other class of biological agents, such as abatacept (selective T-cell costimulator blocker) and Rituximab (Anti-CD 20), were less frequently used. We did not show any statistically significant differences in the types of biological agents used, and did not evaluate their relative toxicity or effectiveness. Payet *et al.*⁽²³⁾ reported that rituximab is less effective in patients older than 75 years.

Our study has several strengths and limitations. It was adequately powered to show statistical differences in our primary analyses, and was conducted in a “real world” setting without strict inclusion and exclusion criteria. Data were collected from two geographically separated sites (Edmonton and Calgary), which arguably makes our results more generalizable. Limitations include the relatively small number of individuals, particularly in the 75+ age group, which limited our ability to assess the impact of factors other than age on the outcomes of interest. As an observational study, we can make no strong claims on causality. We were also restricted to the data elements included in the database and the bDMARDs approved for use by the publically funded drug benefit plan in Alberta at the time of the study. We only used data collected between December 31, 2006 and July 1, 2009. As noted, these dates were chosen to minimize missing data for the variables used in our analyses, but acknowledge that clinical practice has changed substantially over the last ten years.

CONCLUSION

It has been reported that older patients are more likely to experience AEs with the use of biological agents. We confirmed this observation in our study. The effectiveness of biological agents in older populations has been reported to be either similar or worse than what is found among younger patients. We found a higher remission rate among those 75+ compared to RA patients 65–74 years. This needs to be interpreted with caution and requires verification. In the treatment of RA, the clinician must consider the risk/benefit ratio of bDMARDs.

Further research is needed to determine whether patients 75+ are more likely to show remission and whether this, combined with the greater toxicity, should lead to changes in how bDMARDs are prescribed to those 75+.

CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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