Title

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Older Age of Rheumatoid Arthritis Onset and Comorbidities Correlates With Less HAQ-DI and CDAI Response to Etanercept in the RADIUS 2 Registry

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Abstract

Background—Controversy exists in understanding the effects of age of onset and comorbidities in predicting rheumatoid arthritis (RA) response to biologic therapy.

Objective—To investigate the influence of age of onset and number of comorbidities on Health Assessment Questionnaire-Disability Index (HAQ-DI) and Clinical Disease Activity Index (CDAI) responses in active RA patients after 6 months of treatment with etanercept.

Methods—1899 RA patients were assessed after 6 months of etanercept therapy. Patients met the following inclusion criteria: initiated etanercept, continued therapy for at least 6 months, and were not in CDAI low disease activity at baseline (CDAI≤10.0). Changes in HAQ-DI and CDAI scores over 6 months were analyzed across age quintiles. Multivariate regression models evaluated the independent association between both age of onset and number of comorbidities with change in HAQ-DI/CDAI scores or achieving low disease activity, while accounting for other covariates.

Results—Significant improvements in HAQ-DI and CDAI scores were observed in all age-onset groups, although HAQ-DI improvements were less in older-onset patients. Results of multiple linear regression demonstrated that younger age at onset, higher baseline HAQ-DI/CDAI score, rheumatoid factor positivity, shorter disease duration, and fewer comorbidities at baseline were independently associated with improvement in both HAQ-DI and CDAI scores. Similarly, achieving CDAI LDA after ≥6 months of etanercept was associated with younger age of onset, higher baseline CDAI, shorter disease duration, and fewer comorbidities.

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Conflict of Interest:

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Conclusions—Patients with older-onset RA and more comorbidities clinically improved with etanercept, but had lower odds of achieving CDAI LDA. Age of onset and number of comorbidities may be important in determining RA tumor necrosis factor (TNF)-inhibitor response.

Keywords

rheumatoid arthritis; age; outcomes; disease activity; functional status; etanercept

INTRODUCTION

Although older current age may be an easier clinical concept to understand than age at disease onset, several studies specifically examining “age of onset” suggest that this variable in itself portends a different clinical entity [1-3]. Since the 1940s when Schnell and colleagues first described a distinct subset of older-onset rheumatoid arthritis (RA), there has been controversy regarding the classification, treatment, and prognosis of elderly patients with RA [4]. In addition, the definition of older age of onset has been arbitrary in the literature, with age cut-offs ranging between 50 and 75 years.

One third of RA patients are diagnosed at >60 years of age [5]. Patients with older-onset RA are less likely to receive biologic disease-modifying anti-rheumatic drugs (DMARDs) than younger patients, potentially due to concerns about comorbidities, toxicity, side effects, and polypharmacy [6,7]. Remission or low disease activity (LDA) is considered the therapeutic target, which may be difficult for patients with older-onset RA or multiple complex comorbid conditions to achieve[8].

Our objective was to determine the efficacy of biologic therapy in community-treated, older-onset RA patients, with varying number of comorbidities. Combined examinations of randomized controlled clinical trials (RCTs) suggest that TNF inhibitors are generally well tolerated and have similar efficacy in both elderly and younger RA patients [9]. However, few large longitudinal studies of RA have provided a detailed appraisal of age at disease onset as well as number of comorbidities [10].

Therefore, we investigated the impact of age at disease onset and number of comorbidities on functional status and achievement of LDA in a large prospective cohort of RA patients who continued etanercept for at least 6 months.

PATIENTS AND METHODS

Study Population

As described elsewhere, the RADIUS 2 registry is a prospective, real-world, 5-year, multicenter, observational study of 5102 adult patients with moderate to severe RA who enrolled between October 2002 and June 2003, in 390 rheumatology practices across the United States [11-14]. Patients eligible for inclusion in RADIUS 2 were ≥ 18 years old, met the 1987 American College of Rheumatology criteria for RA diagnosis [15], and initiated etanercept at the start of the study. Exclusion criteria included active infection, pregnant or breastfeeding women, known allergy to etanercept or its components, and enrollment in a

clinical trial or other registry with treatments or patient visits imposed by a protocol. Except for the requirement for a patient to receive etanercept at baseline, any biological or non-biological DMARD could be initiated, discontinued, or resumed at the discretion of the investigator throughout the study for RADIUS 2.

The cohort selected for the present study included patients who were enrolled in RADIUS 2, continued etanercept for ≥6 months, maintained stable background DMARD regimen (if any) during that time, underwent a clinical assessment ≥6 months after etanercept initiation, and had Clinical Disease Activity Index (CDAI) >10 at baseline (i.e., patients were not in CDAI LDA or in CDAI remission). Patients who were taking another biologic agent at baseline were excluded.

Assessments

Baseline demographics, comorbidities, and disease characteristics were assessed at study entry, including CDAI [16] and Health Assessment Questionnaire Disability Index (HAQ-DI) (Table 1) [17]. Comorbidities were patient-reported from 17 possible categories.

Rheumatologists determined the frequency of patient visits as clinically indicated. During visits, investigators assessed disease activity, adverse events, and functional status. Study endpoints included changes in HAQ-DI and CDAI scores, and achievement of CDAI LDA (CDAI ≤10) after at least 6 months of follow-up.

Statistical Analysis

Clinical characteristics were compared across the age at disease onset quintiles using one-way analysis of variance (ANOVA) or chi-squared tests (Table 1 and 2). Mean changes in HAQ-DI and CDAI scores over 6 months were compared across the quintiles using ANOVA, adjusted for disease duration at baseline (Table 2). The clinical characteristics that were found to be significant in Table 1 were included in the multivariate models to control for confounding with the age of onset variable. Linear and logistic regression models evaluated the independent association between age at disease onset and the primary study endpoints (Table 3). Additional covariates included baseline CDAI or HAQ-DI as appropriate, rheumatoid factor status, prednisone use, disease duration, gender, comorbidities, and race. In order to assess potential differences in drug safety among older- and younger-onset RA patients, the frequencies of adverse events among patients aged <65 at RA onset and ≥65 years at RA onset were compared using Fisher exact test.

RESULTS

Baseline Characteristics

Patients were divided into 5 quintiles based on age at disease onset: <32, 32–41, 42–48, 49–55, and >55 years. Table 1 lists the baseline characteristics for the 1899 patients who met the inclusion criteria across age of onset quintiles. At study onset through 6-month follow-up, 492 (26%) were on etanercept monotherapy; 309 (16%) on etanercept plus other DMARD; and 1098 (58%) on etanercept plus methotrexate (with or without another non-biologic DMARD).

There were statistically significant differences across age of onset quintiles for gender, race, comorbidities present, disease duration, rheumatoid factor presence, prednisone use, tender joint count, and mean CDAI ($p<0.05$, Table 1). The proportion of patients who were male or had ≥1 comorbidity, increased across age quintiles. Disease duration significantly decreased across age of onset quintiles from 16.5 (SD 12.7) to 4.0 (SD 4.3) ($p<0.001$). Although statistically significant differences were seen in baseline CDAI across the age of onset quintiles (mean 34.7, 36.4, 36.1, 38.0, and 36.9), this was not a clinically meaningful difference across the groups ($p=0.04$)[18].

Improvement in Disease Activity and Function

After 6 months of etanercept treatment, a clinically meaningful decrease in HAQ-DI score (absolute change ≥0.22) was observed in all age-onset quintiles (0.35 ± 0.03 oldest versus 0.48 ± 0.03 youngest, $P = 0.0013$) (Table 2) [19]. Decrease in CDAI scores was robust and similar between quintiles (19.71 ± 0.84 oldest versus 20.13 ± 0.89 youngest, $P = 0.253$). Multiple regression models demonstrated that older age of onset, baseline CDAI/HAQ-DI scores, disease duration, and comorbidities were consistently associated with less improvement in HAQ-DI and CDAI (baseline to follow-up), and lower odds of achieving CDAI LDA at follow-up (Table 3). For every 10 years of age difference in RA onset, patients had a 13% decreased odds of attaining CDAI LDA. In addition, for every additional comorbidity, RA patients had an 18% decreased odd for achieving CDAI LDA.

Adverse Events

In this cohort, adverse events led to discontinuation from the RADIUS 2 study in 0.43% patients with age of onset <65 versus 0.93% of patients with ≥65 age of onset. A Fisher exact test demonstrated that there was not a significant difference in the frequency of adverse events between patients who were less than and those above 65 years at RA of onset ($P = 0.40$).

DISCUSSION

This study investigated the influence of age of RA onset on the effectiveness of TNF inhibitor treatment in routine clinical practice, using a large prospective cohort of moderate to severe RA patients enrolled in the RADIUS 2 registry who received at least 6 months of etanercept therapy. There was a clinically significant improvement in HAQ-DI scores in all age-onset groups, though less pronounced in the older onset quintiles. CDAI improvement was robust for all age-onset groups and met recently published determination of CDAI minimally important difference of >6.0 for all groups[18]. However, regression analyses suggested that older age of onset was independently associated with less improvement in HAQ-DI and CDAI, and less achievement of CDAI LDA.

Overall, the results suggest that older-onset patients benefit from treatment with TNF inhibitors. However, the multivariate regression analyses do imply that onset age has an albeit modest but independently negative impact on therapeutic response when accounting for other variables. Likewise, increasing number of comorbidities has a negative impact on treatment response. Although several studies have evaluated age of onset in RA

crossectionally[6,20,21] and other published reports have evaluated response to therapy in older RA patients [7,22,23], few studies have published data assessing age of onset of RA and response to therapy. One such observational prospective study reported that older patients (age >65) demonstrated less improvement with the disease activity score (DAS28) compared to younger RA patients after treatment with TNF inhibitors [24]. Other studies have shown that HAQ-DI scores in older-onset patients were higher at baseline and improved less with treatment than in younger-onset patients, similar to other studies of elderly RA [25,26].

In our study, 46% of patients had at least one other coexisting medical condition. This number is similar, but slightly lower than reported elsewhere, which ranged from 54% to 60% [27-29]. The number of chronic conditions has been shown to increase with age [30], and it has been suggested to affect the outcome measures in RA irrespective of ongoing disease activity, especially pertaining to physical disability [31,32]. Our group recently published data evaluating number of comorbidities and age (not age of onset) in the CORRONA database [7]. The results suggested that the number of patient reported comorbidities were associated with poorer response outcomes for CDAI and HAQ.

It is plausible that while treatment improves the reversible component of physical disability attributable to the index disease [33], coexisting chronic conditions, such as osteoarthritis, symptomatic cardiovascular disease, and sarcopenia associated with aging [34], may continue to limit physical function in older-onset RA patients. This may partly explain the clinically meaningful HAQ-DI improvement observed throughout all age quintiles, but higher HAQ-DI at baseline and reduced magnitude of HAQ-DI improvement seen in the older age at onset RA patients with treatment.

Although reporting a detailed evaluation of adverse events was beyond the scope of this manuscript, we observed that the rate of adverse events in this cohort leading to discontinuation from the RADIUS 2 trial was similar between patients aged above and below 65 years at RA onset. Several papers have evaluated adverse events in older RA patients with TNF inhibitors and with etanercept. Specifically, a safety assessment of RADIUS 1 and RADIUS 2 was published in 2011, and suggested that age and number of comorbidities were significantly associated with serious adverse events and serious infection risk [12]. A recent study evaluated 11,657 RA patients initiating a TNF inhibitor enrolled in Medicare, Medicaid, or large US health care plans [35]. The authors demonstrated that the rate of serious infections was 1–4 infections per 100 person years higher than that predicted by age, comorbidities, or other factors. The authors also concluded that their study provided reassurance to older patients, or those with comorbidities or other risk factors that they would not be at an increased risk of infection. Another study evaluated 1,808 RA patients enrolled in the British Society of Rheumatology Biologics Register who were treated with TNF inhibitors, and demonstrated that older age was an independent risk factor for serious infections [36]. However, a difference in the relative risk of infection was not seen in the older population. Other papers specifically evaluating etanercept in clinical trials have concluded similar results [23,37].

Within this cohort, the highest quintile for age of onset utilized a cutoff of >55 years. Literature suggests that elderly RA patients and older age of onset can be defined by a very

broad and arbitrary range of age cut-offs of 50–75 years [38-41]. Our group published a paper in 2005 defining elderly RA cohort above the age of 55, as did Milkus et al in another publication [39,40]..Moesmann et al. used an earlier age cut-off of >50 years to describe older RA, and their results suggested that the prognosis for older RA patients was no better than for younger RA patients [42].

The strengths of this study include its prospective design, large patient population, and a unique cohort reflecting RA patients treated in routine rheumatology settings throughout the United States. The study may have a selection bias for patients with good response to etanercept, given that patients were required to continue with treatment for at least 6 months (and treatment could be switched at any time for lack of efficacy). In addition, patients were excluded if they were lost to follow-up within the first 6 months due to inefficacy, adverse events, or other reasons.

In summary, HAQ-DI scores improved less in older-onset patients, possibly due to increased number of comorbidities in this group. Achievement of CDAI LDA was also independently and adversely impacted by age of onset, comorbidities, disease duration, and baseline CDAI score, even after adjusting for other covariates. Therefore, treatment goals should always consider the risk to benefit ratio and be tailored to fit the needs of individual patients.

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TABLE 1

Patient Demographics and Disease Activity at Baseline

Age	Total Cohort n = 1899	≤32.2 y n = 380	>32.2 ≤ 41.3 y n = 380	>41.3 ≤ 48.3 y n = 380	>48.3 ≤ 55.2 y n = 380	> 55.2 y n = 379	*P* value
Female gender, %	77.5	82.4	82.0	75.5	77.0	71.0	<0.001
Non-white race, %	18.2	24.0	19.5	17.6	16.3	13.7	0.005
Comorbidity present, %	45.9	42.3	39.2	44.2	47.9	52.8	0.004
Number of comorbidities (0–17), %							
0	54.1	54.4	60.8	55.8	52.1	47.2	0.1
1	30.3	31.1	25.8	29.2	32.1	33.3	
2	10.8	10.0	9.7	10.5	11.3	12.4	
3	3.4	3.7	2.9	2.9	3.2	4.2	
4	0.9	0.3	0.5	1.3	1.1	1.6	
≥5	0.5	0.3	0.3	0.3	0.3	1.3	
Disease duration, mean years (SD)	8.65 (9.33)	16.5 (12.7)	10.0 (9.0)	7.0 (6.6)	5.7 (5.8)	4.0 (4.3)	<0.001
RF positive, %	1335 (70.3)	63.7	72.9	70.3	73.2	71.5	0.001
Prednisone use, %	996 (52.4)	46.8	55.3	48.4	52.4	59.4	0.003
HAQ-DI, mean (SD)	1.34 (0.67)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)	1.4 (0.7)	1.4 (0.7)	0.14
Physician global VAS, mean (SD)	6.03 (1.76)	6.0 (1.7)	6.1 (1.7)	5.8 (1.8)	6.2 (1.8)	6.0 (1.8)	0.09
Patient global VAS, mean (SD)	6.12 (2.23)	6.1 (2.3)	6.1 (1.7)	6.0 (2.3)	6.2 (2.2)	6.2 (2.2)	0.75
SJC28, mean (SD)	11.37 (6.77)	11.0 (6.7)	11.1 (7.0)	11.2 (6.9)	11.7 (6.5)	11.7 (6.6)	0.36
TJC28, mean (SD)	12.91 (7.97)	11.6 (8.0)	13.1 (8.0)	13.1 (8.0)	13.9 (7.9)	13.0 (7.8)	0.003
Pain VAS, mean (SD)	6.04 (2.31)	6.2 (2.2)	6.2 (2.4)	5.8 (2.3)	6.1 (2.3)	6.0 (2.4)	0.15
CDAI, mean (SD)	36.43 (14.85)	34.7 (15.0)	36.4 (14.9)	36.1 (14.8)	38.0 (15.0)	36.9 (14.4)	0.04

SD, standard deviation; RF, rheumatoid factor; HAQ-DI, Health Assessment Questionnaire Disability Index; VAS, visual analogue scale; SJC28, swollen joint count in 28 joints; TJC28, tender joint count in 28 joints; CDAI, clinical disease activity index.

TABLE 2

Change in Disease Activity Scores From Baseline to Follow-up (Adjusted for Disease Duration at Baseline)

Age	**≤32.2 y n = 380**	**>32.2 ≤ 41.3 y n = 380**	**>41.3 ≤ 48.3 y n = 380**	**>48.3 ≤ 55.2 y n = 380**	**> 55.2 y n = 379**	***P* value**
HAQ-DI Absolute decrease, mean (SE)	0.48 (0.031)	0.49 (0.029)	0.38 (0.029)	0.38 (0.029)	0.35 (0.029)	0.001
CDAI Absolute decrease, mean (SE)	20.13 (0.890)	21.57 (0.814)	19.87 (0.815)	21.64 (0.827)	19.71 (0.837)	0.253
CDAI remission, n (%)	40 (11.1)	35 (9.5)	25 (6.8)	26 (7.1)	24 (6.5)	0.106
CDAI LDA, n (%)	166 (45.9)	168 (45.7)	149 (40.5)	144 (39.6)	141 (38.3)	0.111
SJC28 Absolute decrease, mean (SE)	6.94 (0.383)	7.13 (0.352)	6.43 (0.352)	7.40 (0.357)	7.10 (0.363)	0.393
TJC28 Absolute decrease, mean (SE)	7.50 (0.452)	8.59 (0.415)	8.35 (0.415)	8.64 (0.421)	7.42 (0.427)	0.090
Physician global assessment Absolute decrease, mean (SE)	3.37 (0.126)	3.44 (0.116)	2.99 (0.116)	3.22 (0.117)	2.94 (0.119)	0.013
Patient global assessment Absolute decrease, mean (SE)	2.15 (0.157)	2.28 (0.144)	2.08 (0.145)	2.16 (0.146)	2.02 (0.148)	0.792
Pain VAS Absolute decrease, mean (SE)	−2.68 (0.159)	−2.62 (0.148)	−2.03 (0.147)	−2.24 (0.149)	−2.11 (0.151)	0.009

SE, standard error; HAQ-DI, Health Assessment Questionnaire-Disability Index; CDAI, Clinical Disease Activity Index; LDA, low disease activity; SJC28, swollen joint count in 28 joints; TJC28, tender joint count in 28 joints; VAS, visual analogue scale

TABLE 3

Regression Models for Change in HAQ-DI, Change in CDAI, and CDAI Low Disease Activity

	Change in HAQ-DI		Change in CDAI		CDAI Low Disease Activity	
	Beta-Coefficient (SE)	***P* value**	**Beta-Coefficient (SE)**	***P* value**	**OR (95% CI)***	***P* value**
Age at onset (per 10 years)	0.06 (0.01)	<0.001	0.61 (0.25)	0.016	0.87 (0.79, 0.95)	0.002
Baseline CDAI/HAQ-DI	−0.30 (0.02)	<0.001	−0.68 (0.02)	<0.001	0.96 (0.96, 0.97)	<0.001
Baseline prednisone use (No)	0.02 (0.03)	0.447	0.41 (0.59)	0.484	0.93 (0.76, 1.14)	0.480
Baseline negative RF	0.09 (0.03)	0.002	1.94 (0.70)	0.006	0.80 (0.63, 1.03)	0.081
Disease duration	0.01 (0.00)	<0.001	0.10 (0.04)	0.009	0.98 (0.97, 0.99)	0.004
Female gender	0.09 (0.03)	0.005	1.23 (0.70)	0.080	0.79 (0.62, 1.01)	0.063
Comorbidities	0.05 (0.01)	<0.001	1.28 (0.33)	<0.001	0.82 (0.73, 0.93),	0.001
Non-white race	0.01 (0.03)	0.740	1.12 (0.77)	0.147	0.80 (1.05, 0.61)	0.111

CDAI, Clinical Disease Activity Index; HAQ-DI, Health Assessment Questionnaire; SE, standard error; RF, rheumatoid factor; OR, odds ratio; CI, confidence interval.

* Odds ratio (OR) estimates give the odds of having achieved Low Disease Activity group at 6 months.