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BRIEF REPORT

The influence of age at disease onset on disease activity and disability: results from the Ontario Best Practices Research Initiative

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Abstract This study aims to compare characteristics between late-onset rheumatoid arthritis (RA) and young-onset RA and determine the association between age at disease onset and disease severity. We cross-sectionally studied 971 patients at the time of entry into the Ontario Best Practices Research Initiative, a registry of RA patients followed up in routine care. We restricted patients to ≤5 years of disease duration. Late-onset RA was defined as an onset ≥60 years of age and young-onset RA <60 years. Group differences were compared, and multivariate linear regression models were used to test the influence of age at onset on Disease Activity Score in 28 Joints with erythrocyte sedimentation rate (DAS28-ESR), Clinical Disease Activity Index (CDAI), and Health Assessment Questionnaire (HAQ) scores. The swollen joint count (6.2 vs. 5.3), acute phase reactants (C-reactive protein (CRP) 17.4 vs. 11.8 mg/L, ESR 30.6 vs. 21.5 mm/h), and comorbidity burden were higher in late-onset RA compared to young-onset RA ($p<0.01$). Mean DAS28-ESR (4.6 vs. 4.3) and HAQ (1.2 vs. 1.1) scores were higher in late-onset RA patients ($p<0.05$). Late-onset RA patients received more initial disease-modifying antirheumatic drug (DMARD) monotherapy and corticosteroids in comparison to greater DMARD/biologic combination therapy in young-onset RA patients ($p<0.05$). Adjusted multivariate analyses showed that late-onset RA was independently associated with higher mean DAS28-ESR and HAQ scores, but not CDAI. Late-onset RA patients have greater disease activity that may contribute to disability early in the disease course. Despite this, initial treatment consists of less combination DMARD and biologic use in late-onset RA patients. This may have implications for future response to therapy and development of joint damage, disability, and comorbidities in this group.

Keywords Age of disease onset · Disease activity · Elderly onset · Rheumatoid arthritis

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Introduction

The population of elderly individuals with rheumatoid arthritis (RA) is increasing, and the incidence of RA is increasing in the elderly [1]. An understanding of late-onset RA (LORA) is thus important.

LORA patients often present differently compared to young-onset RA (YORA). Patients with LORA tend less to be female and have a more acute presentation with high inflammatory markers, systemic symptoms, and frequent large joint involvement [2–4].

There is controversy about whether age of onset affects disease activity at presentation or during the initial stages of

disease. Some studies report higher Disease Activity Score in 28 Joints (DAS28) score and less remission in LORA [3–6]. The degree of joint damage has been shown to be higher in LORA, while others report no difference in radiographic progression between YORA and LORA patients [4, 7–10]. Varied results are noted when disease severity is defined in terms of disability, as measured using the Health Assessment Questionnaire (HAQ) [3, 6, 7, 9–12]. Additionally, the types of therapy selected and the effect of treatment influencing these outcomes may differ according to an individual's age at the time of RA onset [5, 13].

The purpose of this study was to compare characteristics of patients with LORA and YORA and test our hypothesis that LORA patients have more severe disease. Our specific aims were to (1) examine differences in patient- and disease-related characteristics between LORA and YORA and (2) assess whether age of onset is independently associated with disease activity and functional status.

Materials and methods

Data source and patients

The Ontario Best Practices Research Initiative (OBRI) is a prospective registry of RA patients that gathers long-term information. Between January 2009 and December 2013, 2179 patients were recruited across 60 sites. OBRI collects voluntary data from both patients and physicians across Ontario, Canada, in community-based and academic practices with minimal loss-to-follow-up or dropout (<5 %). Patients are included if they are ≥18 years of age with a confirmed RA diagnosis. Patients are recruited at any stage of disease and are treated at the discretion of their rheumatologist. Institutional research ethics approval was obtained prior to enrollment.

We restricted our population to individuals who were diagnosed within the last 5 years (N=971) to reflect contemporary clinical practice patterns (e.g., use of biologics, treat-to-target approaches). Since there is no accepted age cutoff for LORA, we used ≥60 years of age at diagnosis to define LORA and <60 years of age to define YORA. Data on age of symptom onset was limited; as such, age of disease diagnosis was used to define age of disease onset.

Clinical assessments

Clinical data in OBRI are obtained from physician visits (occurring at baseline and then as indicated by the physician) and patient telephone interviews at fixed intervals. Disease activity at entry into OBRI is measured using the DAS28 with erythrocyte sedimentation rate (DAS28-ESR) and Clinical Disease Activity Index (CDAI). Functional status is measured using the HAQ.

Cross-sectional demographic and clinical variables, including gender, acute phase reactants, rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA) positivity, and select comorbidities, were obtained at the time of cohort entry. Treatment including previous use (before enrollment) and current use (at the time of enrollment) of disease-modifying antirheumatic drugs (DMARDs) and biologics as well as current corticosteroid use (intramuscular, intra-articular, or oral) was obtained. The first ESR and C-reactive protein (CRP) value within the first 6 months of enrollment was used to calculate the DAS28-ESR and CDAI.

Statistical analysis

Baseline data, stratified according to age of disease onset, are presented, and differences between groups were compared using chi-square tests or Student's t tests, with a p value <0.05 set as the significance level.

The effect of age of onset on disease activity and functional status was estimated by multivariate linear regression analyses. Separate regression models were run using baseline DAS28-ESR, CDAI, and HAQ scores as the dependent variables. For multivariate models, clinically important confounders were selected a priori [gender, disease duration, seropositivity (yes/no), and previous therapy constructed as categorical variables (DMARD monotherapy, biologic monotherapy, or combination therapy with DMARD or biologics)]. Statistical analyses were performed using SAS software, version 9.3.

Results

A total of 971 RA patients were evaluated with 365 patients included in the LORA and 606 patients in the YORA group. The mean disease duration of both groups was under 2 years.

Descriptive data are presented in Table 1. The LORA group had a higher proportion of males with shorter disease duration, and higher swollen joint counts were more often seronegative, with greater ESR and CRP values (p<0.05). The comorbidity profile differed between groups with a significantly greater prevalence of comorbidities in LORA (p<0.0001).

Disease activity based on mean DAS28-ESR score was significantly higher in the LORA group (p<0.004), but the absolute difference was small. In contrast, CDAI scores were similar between groups, including the proportion of patients in CDAI remission and low disease activity state. Mean HAQ scores were statistically higher in LORA patients, although the overall difference between groups was small. Radiographic damage was higher in LORA patients but was not statistically significant, and information on erosive disease at baseline was missing in a fair proportion among both groups (Table 1).

Table 1 Characteristics of RA patients at cohort entry, based on age of disease onset

Characteristics	Late-onset RA *N*=365	Young-onset RA *N*=606	*p* value
Age, years	70.0 (6.3)	47.5 (10.2)	<0.0001
Female, *N* (%)	246 (67.4)	488 (80.5)	<0.0001
Disease duration, years	1.2 (1.3)	1.6 (1.3)	<0.0001
Clinical measures			
Tender joint count-28	6.7 (6.4)	6.6 (6.5)	0.83
Swollen joint count-28	6.2 (5.0)	5.3 (5.1)	0.01
Erosions present of non-missing, *N* (%)	105/290 (36.2)	139/445 (31.2)	0.16
HAQ pain score (0–10 VAS scale)	4.4 (2.7)	4.9 (2.8)	0.001
PtGA (0–10 VAS scale)	4.7 (2.7)	5.2 (2.9)	0.004
PhGA (0–10 VAS scale)	4.5 (2.3)	4.5 (2.5)	0.89
DAS28-ESR score	4.6 (1.4)	4.3 (1.5)	0.004
DAS28-ESR <2.6, *N* (%)	28 (8.1)	85 (14.9)	0.002
CDAI score	22.0 (13.2)	21.8 (14.0)	0.78
HAQ score	1.2 (0.7)	1.1 (0.7)	0.03
Laboratory			
Rheumatoid factor positive of non-missing, *N* (%)	217/346 (62.7)	407/575 (70.8)	0.01
ACPA positive of non-missing, *N* (%)	64/138 (47.4)	165/264 (62.5)	0.001
ESR, mm/h	30.6 (24.6)	21.5 (19.9)	<0.0001
CRP, mg/L	17.4 (11.8)	11.8 (9.9)	<0.01
Comorbidities			
Cardiovascular, *N* (%)	190 (52.9)	99 (16.4)	<0.0001
Diabetes, *N* (%)	48 (13.4)	24 (3.9)	<0.0001
Kidney disease, *N* (%)	15 (4.2)	1 (0.17)	<0.0001
Osteoarthritis, *N* (%)	121 (33.7)	75 (12.4)	<0.0001
Cancer, *N* (%)	38 (10.6)	14 (2.3)	<0.0001
Treatment			
Prior DMARD use, *N* (%)	189 (51.8)	358 (59.1)	0.005
Prior biologic and DMARD, *N* (%)	32 (8.8)	74 (12.2)	0.03
Current corticosteroid	130 (35.7)	148 (24.5)	<0.01
Current DMARD monotherapy	146 (40.1)	195 (32.2)	0.01
Current DMARD combination	155 (42.5)	266 (43.9)	0.66
Current biologic and DMARD combination therapy	28 (7.7)	73 (12.1)	0.03
No DMARD or biologic	16 (4.3)	39 (6.4)	0.18

All values are means (standard deviation) unless otherwise indicated

VAS visual analog scale, *PtGA* patient global health assessment, *PhGA* physician global health assessment, *ACPA* anti-citrullinated protein antibody, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DMARD* disease-modifying antirheumatic drug, *DAS28* Disease Activity Score in 28 Joints, *CDAI* Clinical Disease Activity Index, *HAQ* Health Assessment Questionnaire

A higher proportion of YORA patients reported both previous and current DMARD use as well as combination therapy with DMARD and biologic. Current DMARD monotherapy was greater in LORA compared to YORA patients, with higher use of methotrexate monotherapy in this group (data not shown). Corticosteroids were used by more than one third of LORA patients at baseline, which was significantly higher compared to use in YORA ($p<0.01$).

In multivariate-adjusted models, age at RA onset emerged to be independently associated with DAS28-ESR score, with LORA being associated with a higher baseline DAS28-ESR score (regression coefficient 0.223, 95 % confidence interval 0.02 and 0.43, $p=0.035$). After adjustment for the same confounding variables, baseline CDAI score was not associated with age of disease onset (regression coefficient −0.692, 95 % confidence interval −2.59 and 1.2, $p=0.473$). Age at RA onset was also related to functional status, with LORA being associated with higher baseline HAQ score (regression coefficient 0.142, 95 % confidence interval 0.05 and 0.24, $p=0.004$).

Discussion

In this study, we sought to examine whether age of RA onset affects disease activity and functional status among patients followed up in routine care.

We observed significant differences in clinical characteristics by age of onset and found that LORA was associated with greater disease activity according to DAS28-ESR scores and functional disability. Despite this, LORA patients received less initial DMARD and/or biologic combination therapy, suggesting that a treatment gap exists.

Our findings are comparable to other studies showing a lower female predominance and less seropositivity in LORA [3, 6, 8, 11, 12]. This contrasts previous evidence of elevated RF titers due to increasing age alone; however, seroconversion over time is possible and was not formally assessed in this study [14].

Not surprisingly, a greater burden of comorbidities was seen in LORA patients. This, along with age-related changes in drug metabolism and polypharmacy, has implications on the choice of treatment offered and may partially explain the treatment deficit we and others have observed [5, 6, 12, 13]. Lower rates of combination/biologic therapy use in LORA may reflect patient or prescriber preference about *aggressive* treatment with potential risks in older patients. However, this does not explain the higher corticosteroid use we observed among LORA, which is known to have many potential adverse events. In contrast to our findings, Teoh et al. showed no differences in DMARD or prednisone rates between YORA and LORA but did find a significantly lower rate of nonsteroidal anti-inflammatory drugs (NSAID) in LORA, which they attributed to an awareness of the adverse effects of NSAIDs in older populations [14]. Our study did not examine NSAIDs, and although we cannot verify this with our data, a possible explanation for the higher corticosteroid use in LORA may relate to the need to control severe disease (higher swollen joint counts and inflammatory markers) or possibly treat systemic symptoms (anemia, fever) that are more common in LORA [2, 15]. As this was a cross-sectional study, we do not know whether this treatment differential between groups narrows or persists over time.

We attempted to control for important confounders and found that LORA was independently associated with higher DAS28-ESR scores, which has been confirmed by other cross-sectional analyses [3, 13]. Innala et al. also confirmed the negative effect of LORA on disease activity and demonstrated the persistence of this effect with greater disease activity at 6, 12, and 24 months [5]. On the other hand, Mueller et al. did not find that age of onset affected prognosis over time, possibly because 91.2 % of the LORA group was treated with initial DMARDs, which is higher than treatment estimates in any other report [4].

The choice of disease activity measure may influence results. To our knowledge, this is only the second study to evaluate age of onset and its association with both the DAS28-ESR and the clinically useful CDAI score [16]. We found that the CDAI, an index that omits acute phase reactants, was not significantly different between the groups or independently associated with age of RA onset. This suggests that elevated inflammatory markers seen among LORA patients may drive higher DAS28 scores and influence the proportion of patients that can be categorized in preferred low disease activity or remission states [17].

We also observed age of onset to be associated with HAQ scores. Greater disability has been noted in other studies of LORA [5, 7, 11, 12]. In a study of 1809 early RA patients from Canada, which closely resembles our study population, LORA patients were found to start and end their first year of disease with higher HAQ scores, suggesting that a difference due to age persists over time [6]. While we adjusted our analysis for several important confounders, we did not include comorbid illnesses into our model, which may impact physical function, nor did we evaluate repeated measures of HAQ over time [18]. The clinical significance of the difference in HAQ score between LORA and YORA patients (absolute difference 0.1) is also unclear, especially since it has been suggested that the minimally important clinical difference in HAQ for RA patients is 0.22 [19].

The strengths of our study should be highlighted. The OBRI is a large, representative registry that reflects real-world care and can be generalized to most practices across Canada. We were able to study comorbidities and treatment status, which are not consistently available in other studies. We assessed disease activity by DAS28-ESR and CDAI, which has only been done once before [16]. Weaknesses of this study are linked to the cross-sectional nature of analysis. We could not evaluate patients at the time of symptom onset, diagnosis, or treatment initiation; thus, duration and response to DMARDS prior to cohort entry into OBRI could not be determined and may have influenced our outcomes. We attempted to overcome this by restricting our study sample to those with disease duration of ≤5 years and found that mean disease duration in both groups was only 1.3 years. Information for ACPA and RF was limited due to missing baseline data. This may reflect out-of-pocket expenses incurred by patients to obtain serology testing in some parts of the province. Furthermore, we cannot discern how disease activity, function, and response to drug therapy over time may differ by age of onset or within subgroups (e.g., age of onset 60–70 years vs. onset 70–80 years, etc.), which may be the focus of future investigation. As with any observational study, we had to contend with the possibility of bias and unmeasured confounding that may, in part, explain our results.

In conclusion, LORA patients have different clinical characteristics with greater disease severity at baseline compared

to younger counterparts. Age of disease onset appears to be independently associated with higher baseline disease activity and disability. Despite this, early and initial treatment is less aggressive in LORA and may have implications for future response to therapy and development of comorbidities. Future work exploring factors contributing to treatment gaps and long-term prognosis within subgroups of LORA patients is required.

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Ethical standards This study was approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All persons gave their informed consent prior to their inclusion in the study.

Disclosures None.

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