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BRIEF REPORT

Comparison of Biologic Discontinuation in Patients With Elderly-Onset Versus Younger-Onset Rheumatoid Arthritis

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Objective. The objective of this study is to compare biologic drug discontinuation rates for older- versus younger-onset rheumatoid arthritis (YORA) because this is a key outcome measure that could impact prescribing practices.

Methods. We performed a retrospective medical record review of all patients who fulfilled the 1987 American College of Rheumatology (ACR) criteria for adult-onset rheumatoid arthritis (RA) in 1999-2013 among residents of a geographically defined area, with follow-up until death, migration, or July 1, 2017. Discontinuation rates were estimated using cumulative incidence adjusted for the competing risk of death.

Results. A total of 240 cases of elderly-onset rheumatoid arthritis (EORA) and 366 cases of YORA were identified (65% and 73% female, respectively; $P = 0.025$). Cumulative incidence of biologic initiation was lower among the EORA cohort compared with the YORA cohort (18% vs 33%, respectively, at 10 years after RA incidence; $P < 0.001$). Among those treated with a biologic, years from RA diagnosis to first biologic treatment was not significantly different between the two groups ($P = 0.62$). Drug survival of first biologic was 64% at 1 year (95% confidence interval [CI]: 45%-77%) and 53% at 2 years (95% CI: 33%-66%) for EORA, compared with 61% at 1 year (95% CI: 50%-69%) and 45% at 2 years (95% CI: 34%-53%) for YORA ($P = 0.75$). Concurrent glucocorticoid use at initiation of first biologic was statistically and significantly associated with a lower risk of discontinuation in EORA (hazard ratio 0.21; 95% CI: 0.08-0.53) but not in YORA (interaction $P = 0.04$).

Conclusion. Drug survival rates of biologic medications did not differ significantly between patients with EORA and YORA.

INTRODUCTION

Functional disability is one of the primary outcome measures of rheumatoid arthritis (RA) and is of particular concern for patients who present later in life. Elderly-onset rheumatoid arthritis (EORA) accounts for 10% to 33% of all cases of RA and typically includes those diagnosed after age 60 (1). Compared with patients with younger-onset rheumatoid arthritis (YORA), these patients present with a higher frequency of large-joint involvement, a higher frequency of systemic manifestations, balanced gender distribution, and less seropositive disease (2,3). Appropriate recognition and management of EORA is of increasing importance given the growing proportion of older persons in our population (4).

Although early reports suggested that older patients have a more benign disease course, more recent observational cohorts have shown similar disease activity scores between YORA and EORA and a higher degree of functional decline and joint erosions in EORA (5,6). Treatment of EORA also tends to be less aggressive, with fewer patients receiving conventional and biologic disease-modifying antirheumatic drugs (DMARDs) despite comparable disease severity and duration (7). In those with EORA who do receive biologics, treatment is often delayed in favor of glucocorticoids (5).

Aggressive treatment of RA early in the disease course has been shown to lead to better long-term control (8). Therefore, it is vital to determine whether conservative approaches to treating EORA are justified. There are safety concerns for using biologics in older patients, and less is known about their efficacy given the exclusion of older patients from clinical trials (1). The aim of this study is to compare biologic drug discontinuation rates,

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SIGNIFICANCE & INNOVATION

- Patients with elderly-onset rheumatoid arthritis (EORA) who were prescribed biologic medications were found to have similar drug survival compared with patients with younger-onset rheumatoid arthritis (YORA).
- Concurrent glucocorticoid use at initiation of first biologic is associated with longer drug survival in patients with EORA but not YORA.

as an indirect measure of their efficacy and tolerability, between patients with EORA and YORA.

PATIENTS AND METHODS

Study population and data collection. A population-based cohort of Olmsted County, Minnesota residents aged 18 years and older with incident RA between January 1, 1999, and December 31, 2013, was previously assembled using the resources of the Rochester Epidemiology Project (9). The Rochester Epidemiology Project is a population-based medical records–linkage system that provides access to the complete (inpatient and outpatient) medical records from all medical providers in the community. All patients met the 1987 American College of Rheumatology (ACR) classification criteria for RA and were followed longitudinally until July 1, 2017, death, or migration out of the county. For each patient, the RA incidence date was defined as the earliest date of fulfillment of four or more 1987 ACR criteria for RA. Patients were classified as having YORA if RA was diagnosed before the age of 60 and EORA if RA was diagnosed at age 60 or later.

For each patient, the entire inpatient and outpatient medical records from all providers in Olmsted County were reviewed to obtain data on medication use and potential risk factors for biologic discontinuation. Data on smoking status at RA incidence (never, current, former), height, and weight and results of rheumatoid factor (RF) and anti–cyclic citrullinated peptide antibody (ACPA) tests were also collected by medical record review. Body mass index (BMI) at RA incidence was calculated, and obesity was defined as a BMI greater than or equal to 30 kg/m^2. Data on use of DMARDs and glucocorticoids (ie, start and stop dates as dosages) were collected. Biologic DMARDs included etanercept, infliximab, certolizumab pegol, adalimumab, golimumab, abatacept, rituximab, and anakinra. Biologic discontinuation was defined based on documentation of a discontinuation or switch in the medical record. A minimum gap in time was not used to define discontinuation because each biologic had a different dosing schedule. Temporary discontinuations followed by reintroduction of the same medication were not recorded as discontinuations. The categorization of indications for discontinuation was determined prior to manual chart review, and the mutually exclusive categories were as follows: drug inefficacy, drug allergies or intolerances, achievement of therapeutic goal, infection, patient preference, financial, pregnancy, surgery, and other. Indications for discontinuation were determined by medical record review. Data on the treatment setting and type of practitioner were not collected. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Statistical methods. Descriptive statistics were used to summarize the demographic characteristics of the cohort. Characteristics were compared between EORA and YORA using χ^2 and rank sum tests. The cumulative incidence of first biologic discontinuation, adjusted for the competing risk of death, was estimated for both YORA and EORA. This method censored patients who were still alive at the last follow-up and accounted for those who died before experiencing drug discontinuation to avoid overestimation of the rate of occurrence of discontinuation. The results of these analyses were reported as drug survival (ie, one minus cumulative incidence of drug discontinuation). The analysis was limited to the first biologic course only. Risk factors for biologic discontinuation were examined using Cox models adjusted for age and sex. A P value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Inc) and R 3.2.3 (R Foundation for Statistical Computing).

RESULTS

Of 606 patients diagnosed with RA during the study period, 156 were treated with any biologic DMARD. This included 116 patients with YORA and 40 patients with EORA. Cumulative incidence of biologic initiation was lower among patients with EORA compared with YORA (18% vs 33%, respectively, at 10 years after RA incidence; $P < 0.001$). Both cohorts were predominantly female (YORA: 73%; EORA: 63%; $P = 0.20$), and there were no statistically significant differences in RF or ACPA positivity, smoking status, BMI, or time from RA diagnosis to first biologic treatment between age groups. Most patients were taking at least one conventional DMARD at the time of starting their first biologic (YORA: 84%; EORA: 92%), with methotrexate being the most commonly used agent (YORA: 65%; EORA: 68%). Fifty-seven percent of patients with YORA and 68% of patients with EORA were prescribed glucocorticoids concurrently with their first biologic ($P = 0.24$).

The individual biologics used in each group are listed in Table 1. Tumor necrosis factor inhibitors (TNFis) represented the large majority of biologics in each group, although specific agents differed significantly. Etanercept was the most commonly used first biologic for YORA and EORA (47% and 30%, respectively). Infliximab was the second most common biologic. The

Table 1. Patients with incident RA diagnosed in 1999-2013 who have been treated with a biologic

	YORA (n = 116)	EORA (n = 40)	*P*
Age at RA diagnosis, mean (SD), y	43.7 (8.8)	67.1 (5.4)	<0.001
Sex (female), n (%)	85 (73)	25 (63)	0.20
Years from RA to first biologic, mean (SD)	2.8 (3.5)	2.1 (2.7)	0.62
RF positivity, n (%)	79 (68)	30 (75)	0.41
ACPA positivity, n (%)	60 (58)	24 (69)	0.28
RF/ACPA positivity, n (%)	84 (72)	34 (85)	0.11
Ever smoker, n (%)	59 (51)	21 (53)	0.86
BMI (kg/m^2) at RA diagnosis, mean (SD)	30.7 (7.2)	29.8 (7.4)	0.41
Any concurrent glucocorticoids used at initiation of first biologic, n (%)	66 (57)	27 (68)	0.24
Concurrent MTX use at initiation of first biologic, n (%)	75 (65)	27 (68)	0.74
Concurrent HCQ use at initiation of first biologic, n (%)	35 (30)	15 (38)	0.39
Drug name of first ever biologic, n (%)			0.037
Etanercept	54 (47)	12 (30)	...
Infliximab	21 (18)	9 (23)	...
Anakinra	1 (1)	0 (0)	...
Abatacept	4 (3)	4 (10)	...
Rituximab	3 (3)	4 (10)	...
Certolizumab pegol	23 (20)	6 (15)	...
Adalimumab	10 (9)	3 (8)	...
Golimumab	0 (0)	2 (5)	...

Abbreviation: ACPA, anti–cyclic citrullinated peptide antibody; BMI, body mass index; EORA, elderly-onset rheumatoid arthritis; HCQ, hydroxychloroquine; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; YORA, younger-onset rheumatoid arthritis.

distributions of first biologics used differed between YORA and EORA (*P* = 0.04).

The time trends for first biologic drug survival are shown in Figure 1. Drug survival of the first biologic was 64% at 1 year (95% confidence interval [CI]: 45%-77%) and 53% at 2 years (95% CI: 33%-66%) for EORA, compared with 61% at 1 year (95% CI: 50%-69%) and 45% at 2 years (95% CI: 34%-53%) for YORA (*P* = 0.75). Limiting the analysis to patients who received TNFis yielded similar results, with no significant differences between the two groups. An analysis on non-TNFi biologics showed drug survival of 31% at 1 year (95% CI: 2%-52%) and 19% at 2 years (95% CI: 0%-37%) for EORA, compared with 64% at 1 year (95% CI: 43%-77%) and 57% at 2 years (95% CI: 36%-71%) for YORA (*P* = 0.004). Changing the age cutoff for EORA to 65 did not result in any statistically significant differences in drug survival between groups.

Among 86 and 29 patients with YORA and EORA, respectively, who discontinued their first biologic during follow-up, the most common reason for first biologic discontinuation in both groups was drug inefficacy (YORA: 48%; EORA: 31%), followed by drug allergies or intolerances (YORA: 14%; EORA: 17%), achievement of therapeutic goal (YORA: 12%; EORA: 17%), and infection (YORA: 10%; EORA: 10%). Differences between groups were not statistical significance (*P* = 0.49). Potential risk

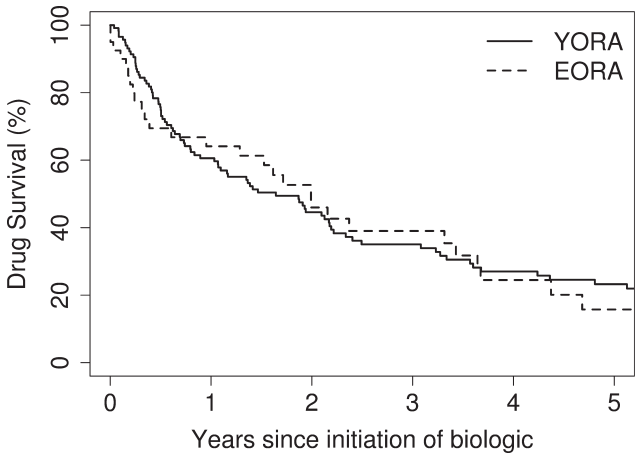

Figure 1. Drug survival for time from start of first biologic to discontinuation, adjusted for competing risk of death. EORA, elderly-onset rheumatoid arthritis; YORA, younger-onset rheumatoid arthritis.

factors for first biologic discontinuation are shown in Table 2. There were no significant risk factors identified for patients with YORA, whereas concurrent glucocorticoid use at initiation of the first biologic (hazard ratio [HR] 0.21; 95% CI: 0.08-0.53) and obesity (HR 0.28; 95% CI: 0.11-0.69) were associated with a lower risk of discontinuation in EORA.

DISCUSSION

Our objective was to examine the impact of age at RA diagnosis on the use of biologic DMARDs in RA. EORA was associated with a lower cumulative incidence of biologic use during the study period. Among patients started on a biologic, there were no significant differences in baseline features, including rates of seropositivity, smoking status, obesity, and time from RA diagnosis to first biologic treatment among biologic users, or in the time to discontinuation when comparing YORA with EORA. Concurrent glucocorticoid use at biologic initiation and obesity at RA diagnosis were protective against discontinuation for EORA, but no other significant risk factors were identified in either group.

These data add further support to previous observational studies showing that patients with EORA are less likely to receive biologic therapy despite similar levels of disease activity (5,7). There are several potential explanations for this. Foremost is the concern for higher rates of infection and other adverse events in older patients. Although reasons for drug discontinuation in this cohort suggested similar rates of serious adverse events, the sample size may not have been large enough to detect small differences. Previous studies have shown that age is a risk factor for serious infections in patients receiving TNFi therapy (10). This additional risk of advanced age may be small, however, with one cohort showing an adjusted HR for serious infections of 1.036 and an overall rate of 31.8 serious infections per 1000 patient-years (11).

Table 2. Risk factors for biologic discontinuation

Parameter	YORA, HR (95% CI)	EORA, HR (95% CI)	Interaction *P*
Male sex	0.84 (0.51-1.37)	0.73 (0.29-1.81)	0.96
Years from RA to first biologic	0.98 (0.91-1.05)	1.00 (0.85-1.18)	0.70
RF/ACPA positivity	0.90 (0.55-1.45)	0.49 (0.14-1.64)	0.49
Ever smoker	0.89 (0.57-1.39)	0.93 (0.44-2.00)	0.87
Obesity (BMI ≥ 30) at RA diagnosis	0.99 (0.64-1.53)	0.28 (0.11-0.69)	0.032
Any concurrent glucocorticoids used at initiation of first biologic	0.80 (0.52-1.24)	0.21 (0.08-0.53)	0.044
Count of unique prior DMARDs discontinued by initiation of first biologic	0.98 (0.78-1.21)	0.95 (0.61-1.46)	0.83
Count of concurrent DMARDs used at initiation of first biologic	0.90 (0.63-1.29)	0.58 (0.27-1.21)	0.44
Any concurrent MTX use at initiation of first biologic	0.70 (0.45-1.11)	1.07 (0.47-2.47)	0.37
Any concurrent HCQ use at initiation of first biologic	1.30 (0.82-2.06)	0.66 (0.29-1.48)	0.22
Any concurrent other DMARD use at initiation of first biologic	0.84 (0.38-1.88)	0.66 (0.25-1.76)	0.75

Abbreviation: ACPA, anti–cyclic citrullinated peptide antibody; BMI, body mass index; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; EORA, elderly-onset rheumatoid arthritis; HCQ, hydroxychloroquine; HR, hazard ratio; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; YORA, younger-onset rheumatoid arthritis.

Economic factors may also contribute to treatment patterns in EORA. Patients often rely on Medicare for health insurance once they reach the age of 65, which could affect drug selection for older patients. This likely explains the finding of a higher rate of infliximab use for EORA. Infliximab, an infusion drug, is more commonly reimbursed by Medicare compared with self-injectables such as etanercept and adalimumab (12,13). This confounds many previous observational studies comparing the efficacy and adverse effects of different TNFis. Infliximab may be associated with infusion reactions and higher rates of immunogenicity, although the higher reported discontinuation rates could be in part due to channeling of higher-risk patients (such as the elderly and those who cannot self-administer medications) toward this drug (14).

Glucocorticoid use at the time of starting a first biologic was associated with longer drug survival in patients with EORA. This is most likely due to additive immune suppression making persistent disease activity less likely. It is less clear why this trend was attenuated in younger patients, particularly given the similar rates of concurrent steroid use at biologic initiation. Previous studies have shown that older patients with RA are treated more frequently with glucocorticoid monotherapy, and it is possible that EORA represents a more glucocorticoid-responsive variant of the disease in some cases. The inverse association between obesity and risk for discontinuation may be due to higher rates of erosive disease in patients with low BMI because prior studies have shown a lower risk of radiographic disease progression in early RA among patients with obesity (14).

Our study reflected a real-world experience of biologic discontinuation, with similar baseline characteristics between groups, long-term follow-up data, and control for multiple potential confounding variables, including risk for death in older patients. Limitations include those that apply to any retrospective observational study. It is not possible to say whether the lack of differences seen in drug survival reflect comparable baseline risks for discontinuation because patients with EORA may be selected for biologic therapy based on their individual comorbidities and disease severity. The cohort size may also limit our ability to detect smaller differences or risk factors in drug discontinuation or differences between individual biologic drugs. In addition, this patient population represents a single geographically defined area, which may limit generalizability to more diverse populations.

This study showed no differences in biologic drug discontinuation rates between patients with YORA and EORA. This is an important finding given the concern some clinicians may have about prescribing biologics for EORA. Recent studies describe similar levels of disease severity between age groups and higher rates of functional impairment in EORA. Certainly, the benefits of biologic therapy must be balanced with the potential adverse effects, although current evidence may not justify the trend of less frequent biologic use for EORA. Determining whether the results of improved disease control in older patients counterbalance the risks associated with biologic therapy is an important area for further research.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, approved the final version to be published, and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Richter, Matteson, Crowson.
Acquisition of data. Richter, Matteson, Davis.
Analysis and interpretation of data. Richter, Matteson, Davis, Achenbach, Crowson.

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