Does Age Bias the Aggressive Treatment of Elderly Patients with Rheumatoid Arthritis?

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ABSTRACT. ***Objective.*** Age bias has been reported to result in undertreatment of elderly patients with various medical conditions. We investigated whether a similar bias exists in the treatment of elderly patients with rheumatoid arthritis (ELDRA) compared to matched younger controls (YRA).

Methods. We performed an analysis of our RA clinical research registry to determine whether any differences exist between ELDRA and YRA patients with respect to use of combination disease modifying antirheumatic drugs (DMARD), biologic agents, corticosteroids, and nonsteroidal antiinflammatory drugs (NSAID). We also determined whether any difference in clinical status could be identified.

Results. Forty-nine female ELDRA subjects (age > 70 yrs) with insurance were matched for sex, insurance status, and duration of disease to YRA subjects (< 60 yrs). No statistically significant difference was noted in number of DMARD currently in use (1.24 ± 0.78 vs 1.24 ± 0.69, $p = 1.00$), or number of patients using biologic agents (25 vs 30; $p = 0.31$), corticosteroids (16 vs 11; $p = 0.26$), or NSAID (26 vs 36; $p = 0.06$). ELDRA and YRA patients also reported similar pain (judged using a visual analog scale, VAS; 3.5 ± 2.6 cm vs 3.4 ± 2.2 cm), fatigue (VAS 3.2 ± 2.7 cm vs 3.9 ± 2.9 cm), global assessment (VAS 2.8 ± 2.2 cm vs 3.5 ± 2.6 cm), and Health Assessment Questionnaire disability scores (0.82 ± 0.5 vs 0.73 ± 0.5).

Conclusion. In this cohort of elderly patients with RA, we detected no bias in the use of RA treatment compared with younger controls. Clinical RA measures also showed that these elderly patients with RA were faring at least as well as the younger controls; they were not relatively undertreated. (J Rheumatol 2005;32:1243–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   ELDERLY   AGE BIAS
DISEASE MODIFYING ANTIRHEUMATIC DRUGS   BIOLOGIC THERAPY

As the population ages and life expectancy increases, rheumatologists will be confronted with the task of treating greater numbers of elderly patients with rheumatoid arthritis (RA). An aggressive therapeutic approach, including early intervention with disease modifying antirheumatic drugs (DMARD), administration of higher doses of DMARD, and use of combination DMARD therapy, has become the standard of care for RA regardless of age. However, many age related factors make management of the elderly population with RA a therapeutic challenge. For example, the elderly often have several medical conditions and take multiple medications, placing them at potentially greater risk for drug related adverse effects secondary to both compounded comorbidity and polypharmacy. Renal

and hepatic changes that occur as a natural part of aging may alter drug metabolism. Further, the senescent immune system in the elderly may make them more vulnerable to complications of immunosuppression that results from RA treatment[1].

Little is known regarding whether the elderly RA population is treated differently from younger patients with RA with respect to class and doses of antirheumatic drugs, especially the newer biologic agents. Despite the general natural history of aging, not all older patients experience these age related changes. Nor is there any evidence that these changes translate into clinically important differences with respect to RA therapy. Only one study has been published that addresses whether use of aggressive RA therapy, specifically biologic agents, results in different efficacy and safety outcomes in the older versus younger RA patient[2]. It has been speculated that elderly RA patients are treated less aggressively than younger ones. This speculation may be due to a perceived increased risk of medication side effects or adverse events that has been reported for other chronic diseases[3-6].

We compared current use of RA medications in elderly and younger patients with RA. We then compared the clinical status of these 2 populations to determine whether the elderly were undertreated.

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MATERIALS AND METHODS

Subjects. We conducted a secondary analysis of prospectively collected data from the Hospital for Special Surgery Rheumatoid Arthritis Clinical Research Registry. The registry is an Institutional Review Board approved, HIPAA (Health Insurance Portability and Accountability Act) compliant prospective, observational, longitudinal database of clinical information collected at regular intervals from RA patients and their rheumatologists. All subjects were seen by a rheumatologist on at least 2 occasions at our tertiary care institution before they were enrolled in the registry.

Patients meeting 1987 American College of Rheumatology (ACR) criteria for the classification of RA are included in the registry. Baseline patient interviews are conducted at the time of the patient's routine office visit. Corresponding followup formats of these questionnaires are administered to patients every 6 months on a continuing basis. These interviews are complemented by regular, standardized medical record review and physician queries to obtain laboratory and imaging data, and to confirm information provided by the study subjects. Data include demographics, RA-specific history, general medical and surgical history, use of RA and non-RA medications, clinical assessment of disease activity (e.g., morning stiffness, joint pain), and functional disability as measured by the multidisciplinary Health Assessment Questionnaire (HAQ).

During an 18 month period from September 2001 through February 2003, 273 patients with RA were recruited and provided informed consent to participate in the registry. The current study is based on the data on these 273 registry subjects. For our first analysis, we grouped patients according to age. Elderly was defined as age > 70 years at the time of the initial interview. Thus, elderly RA (ELDRA) patients included both elderly onset and younger onset disease. Patients under age 60 years constituted our "young" RA (YRA) population. A 10 year gap was allowed between patient groups in order to establish a true distinction between the 2 populations.

Female ELDRA subjects were matched to YRA patients (aged 20–60) for duration of disease ± 3 years. Exclusion criteria included patients without private insurance and thus restricted access to certain medications, notably the biologic agents. Those subjects with > 35 years of disease were excluded, as the feasibility of matching these subjects to younger patients on the basis of disease duration would be problematic. Male patients were not included as there were very few in the ELDRA category (n = 8), half of whom had > 35 years of disease (see below). We compared use of RA medications and clinical status at the time of the initial registry interview.

Classification of medication. RA-specific medications were examined as 3 distinct categories: DMARD, corticosteroids, and nonsteroidal antiinflammatory drugs (NSAID). DMARD included hydroxychloroquine, sulfasalazine, gold, methotrexate (MTX), azathioprine, cyclosporin A, mycophenolate mofetil, leflunomide, etanercept, infliximab, adalimumab, and anakinra. Two subgroups of DMARD were also considered for our analysis, conventional medications and biologic agents. Biologic agents included etanercept, infliximab, adalimumab, and anakinra. Tumor necrosis factor inhibitors included all biologics except anakinra. Only oral corticosteroid use was evaluated. NSAID included the COX-2 inhibitors, celecoxib, rofecoxib, and valdecoxib. However, a separate analysis of COX-2 inhibitors only was also conducted.

Data analysis. Initial descriptive analyses of the baseline demographic and clinical variables of ELDRA patients were compared to those of the YRA group. Nominal variables were compared using chi-square or Fisher's exact test. Ordinal variables were compared using Mann/Whitney or Wilcoxon tests. Continuous variables were compared using paired Student t test. Our primary outcome, use of RA medications, was assessed in 4 ways: number of DMARD currently in use, number of patients currently using steroids, NSAID, and biologic therapy. Statistical significance was corrected for multiple comparisons and set at p = 0.0125 (0.05 divided by 4 outcomes).

RESULTS

Demographic and baseline data. Of the 273 RA patients included in the registry at the time of our analysis, we iden-
tified 49 who met criteria for ELDRA and matched them to 49 YRA patients (Table 1). Mean age of the ELDRA group was 76.1 ± 4.1 vs 46.8 ± 11.1 years in the YRA group (p < 0.001). Charlson Comorbidity Index scores were also significantly higher in the ELDRA patients compared to the YRA patients (2.33 ± 1.7 vs 1.55 ± 0.76; p = 0.004). Otherwise, these 2 populations were similar with respect to ethnicity, marital status, and education (Table 1).

There was no difference between the 2 age groups with respect to the duration of RA, 11.3 ± 10.1 vs 11.1 ± 9.7 years, respectively (p = 0.11), indicating that our matching procedures were successful. Thirty-six (73.5%) of the ELDRA subjects had elderly-onset RA (diagnosis after age 60) and 13 (26.5%) had RA that developed when they were younger. Other baseline RA characteristics were also similar, including number of ACR criteria per patient (p = 0.48) and total number of extraarticular manifestations (p = 0.52). Prevalence of clinical features that are associated with poorer outcome was similar when ELDRA were compared to YRA. These included rheumatoid nodules (57% vs 63%; p = 0.54), rheumatoid factor positivity (79% vs 71%; p = 0.61), and presence of erosive disease (63% vs 57%; p = 0.24). No difference in number of joints replaced or number of subjects with joint fusions was detected.

Medication use. ELDRA and YRA groups were similar with respect to mean number of DMARD currently in use (1.24 ± 0.78 vs 1.24 ± 0.69, respectively; p = 1.00) and mean number of failed DMARD (1.80 ± 1.6 vs 1.80 ± 1.7; p = 1.00). The number of ELDRA compared to YRA patients using combination therapy also did not differ significantly [14 (29%) vs 20 (41%); p = 0.29]. Distribution of specific DMARD in use at the time of the interview is shown in Table 2. Interestingly, there was a difference in current use of MTX, with fewer YRA patients using the drug (55% vs 31%; p = 0.014). However, among those subjects currently using MTX, there was no difference in dose (10.7 ± 7.4 mg vs 12.2 ± 4.7 mg, respectively; p = 0.64).

Comparison of the number of ELDRA and YRA patients currently using biologic therapy showed no statistically significant difference [25 (51%) vs 30 (61%), respectively; p = 0.31]. Among the biologic agents, fewer ELDRA patients had ever used etanercept than did YRA patients [17 (35%) vs 29 (59%)]. Similarly, the current use of etanercept was less common within the ELDRA group compared with the YRA group (9 vs 19). The converse was found to exist for infliximab. A greater number of ELDRA patients had ever used infliximab [20 (41%) vs 14 (29%)] and its current use was more common for this group as well (15 vs 11). A single ELDRA patient was using adalimumab at the time of the analysis. Anakinra was not used by any subject.

Rates of discontinuation for each DMARD are also shown. Reasons for discontinuation have been categorized based on reported reason for discontinuation, including inefficacy, adverse event or side effect, and other. A breakdown

Table 1. Comparison of baseline characteristics between ELDRA and YRA patients.

Characteristic	ELDRA	YRA	p
Age at interview, yrs, mean (SD)	76.1 (4.1)	46.9 (11.1)	< 0.001[†]
Charlson Comorbidity Index, mean (SD)	2.33 (1.7)	1.55 (0.8)	0.004[†]
Duration of RA, yrs, mean (SD)	11.3 (10.1)	11.1 (9.7)	0.11
No. of ACR criteria per patient, mean (SD)	5.37 (1.3)	5.53 (1.0)	0.48
No. of extraarticular manifestations, mean (SD)	0.59 (0.8)	0.47 (0.9)	0.52
Rheumatoid nodules, n (%)	28 (57)	31 (63)	0.68
Rheumatoid factor positive, n (%)	39 (79)	35 (71)	0.61
Radiographic erosions, n (%)	31 (63)	28 (57)	0.68
No. of joint replacements, mean (SD)	0.73 (1.5)	0.47 (1.0)	0.31
Range	0–7	0–4	
Subjects with joint fusions, n (%)	7 (14)	6 (12)	0.77

Continuous data are compared by paired Student t test. Categorical data were compared using chi-square or Fisher's exact test, as appropriate. [†] Statistically significant.

Table 2. Comparison of DMARD history between ELDRA and YRA subjects: use and discontinuation, n (%)[1].

	Ever Used[2]		Currently in Use[2]		Discontinued Due to Adverse Event or Side Effect		Discontinued Due to Inefficacy		Discontinued for Other Reason[3,4]	
	ELDRA	YRA	ELDRA	YRA	ELDRA	YRA	ELDRA	YRA	ELDRA	YRA
Hydroxychloroquine	27 (55)	29 (59)	3 (6)	7 (14)	3 (11)	7 (24)	19 (70)	11 (38)	2 (7)	4 (14)
Sulfasalazine	9 (18)	17 (35)	1 (2)	2 (4)	3 (33)	4 (24)	4 (44)	8 (47)	1 (11)	3 (18)
Gold	20 (41)	20 (41)	1 (2)	4 (8)	10 (50)	3 (15)	8 (40)	11 (55)	1 (5)	2 (10)
Methotrexate	41 (84)	25 (51)	27 (55)	15 (31)	11 (27)	2 (8)	1 (4)	5 (20)	2 (4)	3 (12)
Leflunomide	10 (20)	9 (18)	3 (6)	3 (6)	3 (30)	2 (22)	3 (30)	3 (33)	1 (10)	1 (11)
Cyclosporine	1 (2)	2 (4)	0 (0)	0 (0)	1 (100)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Etanercept	17 (35)	29 (59)	9 (18)	19 (39)	2 (12)	2 (7)	4 (24)	6 (21)	2 (12)	2 (7)
Infliximab	19 (39)	14 (29)	15 (31)	11 (22)	3 (16)	2 (14)	1 (5)	1 (7)	0 (0)	0 (0)

[1] Mycophenolate mofetil and azathioprine were each used for the treatment of one patient in the ELDRA group. No subject in either group had used anakinra at the time of the analysis. [2] Percentages calculated based on total population (n = 45). [3] Percentages calculated based on number of subjects who had ever used the particular DMARD. [4] Other reasons for discontinuation may include pregnancy, cost/insurance, patient preference, and others.

of adverse events and side effects with each DMARD is provided in Table 3. Unfortunately, due to the way in which data are recorded in the registry it is not possible to determine if these events occurred in the ELDRA group prior to becoming elderly. Therefore, we cannot compare rates of these events between elderly and younger subjects with RA.

The number of patients currently being treated with corticosteroids was no different for ELDRA compared to YRA subjects [16 (33%) vs 11 (22%), respectively; p = 0.26]. Nor was there any difference in the mean daily dose of corticosteroids among those patients currently using the drug (6.0 ± 4.0 mg vs 7.0 ± 3.0 mg; p = 0.50). Similar results were found when comparing the use of NSAID including COX-2 inhibitors [26 (53%) vs 36 (73%); p = 0.06]. Surprisingly, only 9 (18%) ELDRA subjects were currently using a COX-2 inhibitor compared to 22 (45%) of the YRA subjects (p = 0.009).

Clinical RA status. Current clinical status of RA as reported by subjects at the time of the interview was similar for both ELDRA and YRA patients with respect to pain, fatigue, global assessment of disease activity, and HAQ scores (Table 4).

It should also be noted that HAQ scores were extremely low for both ELDRA and YRA groups, suggesting little to no disability (0.82 ± 0.5 vs 0.73 ± 0.5; p = 0.27).

DISCUSSION
Rheumatoid arthritis has traditionally been thought of as an inflammatory arthritis of the young and middle aged. Original investigations concluded the mean age of onset of RA to be around 40 years[7-9]. Subsequent studies have noted a steady increase in mean age at onset of RA, and have showed a steady trend with respect to age at initial diagnosis. The mean age at diagnosis among Finnish patients was 48.9 ± 13.4 years in 1975 and increased to 57.8 ± 14.8 years (p < 0.001) by 1990[10]. Additionally, Linos, *et al*[11] reported that among RA patients with data maintained in the Olmsted County (Minnesota, USA) medical database from 1950 to 1974, overall incidence of RA was 48.8 cases per 100,000. Age-specific incidence was highest among the oldest age cohorts: 142.1 cases per 100,000 in the group aged 60–69 years and 157.6 cases per 100,000 among those 70 years and older.

Table 3. Description of adverse events and side effects contributing to the discontinuation of specific DMARD*.

DMARD	ELDRA (n)	YRA (n)
Hydroxychloroquine	GI upset (2), unknown (1)	GI upset (4), dermatologic (1), ocular (1), unknown (1)
Sulfasalazine	GI upset (1), dermatologic (1), general discomfort (1)	GI upset (3), dermatologic (1)
Gold	GI upset (1), dermatologic (5) proteinuria (1), oral sores (1), hematologic (1), allergic (1), unknown (1)	Dermatologic (2), allergic (2)
Methotrexate	GI upset (4), dermatologic (1), alopecia (3), weight loss (1), oral sores (1), fatigue (1), liver (2), lung (2), hematologic (2), lymphoma (1), allergic (1)	GI upset (2), liver (1)
Cyclosporine	Unknown (1)	Hypertension (1), headache (1), unknown (1)
Etanercept	Infection (1), unknown (1)	Dermatologic (1), infection (1)
Infliximab	Infection (2), lung (1), allergic (1)	Dermatologic (1), lung (1), allergic (1)

* Totals may be greater than numbers cited in previous table as some patients experienced more than a single side effect/adverse event. GI: gastrointestinal.

Table 4. Comparison of clinical status of RA between ELDRA and YRA patients.

Clinical Variable	ELDRA	YRA	p
Pain VAS, cm, mean (SD)	3.5 (2.6)	3.4 (2.2)	0.88
Fatigue VAS, cm, mean (SD)	3.2 (2.7)	3.9 (2.9)	0.28
Global assessment VAS, cm, mean (SD)	2.8 (2.2)	3.5 (2.6)	0.12
Presence of morning stiffness, n (%)	43 (88)	43 (88)	1.00
HAQ disability score, mean (SD)	0.82 (0.5)	0.73 (0.5)	0.27

VAS: visual analog scale, HAQ: Health Assessment Questionnaire.

In addition to the shift in RA epidemiology, the US Bureau of the Census reports a shift in age distribution and life expectancy[12]. It is projected that while the number of Americans over the age of 65 was 35.0 million (12.4%) in the year 2000, this number will increase to 39.7 million by 2010, 53.7 million by 2020, and 70.3 million or 20% of the US population by 2050. Furthermore, whereas life expectancy of the average 65-year-old in 1995 was 15.5 years, projected life expectancy of the same age cohort in 2005 is 20.3 years.

The net result of these RA-specific and secular trends is an increase in the number of elderly with RA. Thus, rheumatologists must be prepared to offer this medically vulnerable population the best possible treatment options to maximize their clinical outcome and overall quality of life.

Very little is known regarding the treatment of the elderly patient with active RA. Part of the reason is that until recently RA was a rapidly destructive and disabling disease that only required supportive therapy if and when the patient reached old age. Additionally, life expectancy of the RA patient was significantly shorter than control subjects matched for sex and year of birth[13-16]. Finally, the perception of the older patient as being frail and unable to tolerate common medical therapies as well as younger adults, i.e., age bias, is a common problem in many disease populations.

Age bias has been reported for congestive heart failure[17], coronary artery disease including myocardial infarction[3], hypertension[4], lung cancer[5], and breast cancer[6]. Hajjar, *et al*[4] reported that physicians often believe the risks of treatment for chronic disease among the elderly, in this case hypertension, outweigh their benefits, especially if the condition is perceived to be a natural part of aging. Because the prevalence of osteoarthritis is high among the elderly, the symptoms of arthritis in general (e.g., pain, fatigue, stiffness) have the potential to be understood by physicians and patients as expected in the course of growing old. Thus, it would not be surprising for underrecognition of RA symptoms and their seriousness to result in undertreatment of the elderly patient with RA.

While treatment disparities based on age bias are a serious issue, some perceptions about the elderly regarding the risks and benefits of specific drugs may be true. Studies of

the biology of aging suggest changes within the aging immune system could potentially place the elderly RA patient at risk for complications secondary to aggressive RA therapy with DMARD, especially biologic agents. Associations between immune senescence and infection are implied by the increased incidence of the reactivation of tuberculosis and the increased death rates due to infections including pneumonia, influenza, tetanus, and infectious endocarditis[1]. Consequently, fear of increased immunosuppression and increased susceptibility to serious infections may also result in undertreatment of elderly with active RA.

In this cohort of elderly female patients with RA, use of aggressive RA therapy, i.e., combination DMARD therapy and use of biologic agents, was not different compared to that of matched younger controls. The same was true for use and dose of corticosteroids and use of NSAID including COX-2 inhibitors. Thus, unlike the findings of studies in cardiology and oncology, we have no evidence that age biases physicians' therapeutic approach to RA in our tertiary care center. Specifically, these rheumatologists do not appear to avoid the use of multiple and/or more potent agents among the elderly.

We did identify a difference in the current use of MTX. This is likely due to the recommendation for the concomitant use of MTX with infliximab, which was prescribed more often among the ELDRA patients compared to the YRA group. The proportion of ELDRA patients using etanercept compared to infliximab was the inverse of that found for YRA patients. This difference may be attributable to third-party coverage of patients 65 years and older by Medicare for infliximab infusions and not for etanercept.

Although no difference was found in the use of NSAID including COX-2 inhibitors, significantly more YRA patients were receiving COX-2 inhibitors compared to those with ELDRA. This is surprising, as the elderly are more likely to be at greater risk for gastrointestinal bleeding associated with conventional NSAID use. Reports of the potential increased risk for cardiovascular events with COX-2 inhibitor use may account for the difference. Further, the increased cost of COX-2 inhibitors compared with conventional NSAID may also contribute to this disparity.

Measures of disease activity and disability were also similar between the 2 study groups, and indicate that the elderly subjects are faring at least as well as the younger controls. In other words, we found no evidence that this cohort of ELDRA patients is undertreated.

Unfortunately, the cross-sectional design of this analysis, the time of recruitment and interview of patients into the registry (i.e., not an inception cohort), and the data collection methods used for the registry did not allow evaluation of the difference in response to RA therapy by ELDRA compared to YRA subjects. Plans are under way to conduct prospective evaluations to answer this question.

Despite these findings, this study cannot conclude that

age bias does not exist for all ELDRA populations. These are patients seen at a tertiary care center, which itself has likely introduced a selection bias. Tertiary care centers usually select for the sickest patients. However, the cohort in this study was exceptionally healthy with respect to both RA and overall health, as evidenced by the low HAQ scores and Charlson comorbidity scores. Thus, the generalizability of the results is unclear. At the very least we can conclude that in elderly female patients with RA with minimal infirmity and access to medication, our rheumatologists do not perceive any increased risk for use of aggressive RA therapy.

The very low HAQ scores reported by our population are somewhat surprising, considering the mean duration of disease and the inherent selection bias for more seriously ill patients attending a tertiary care center. Over the past several years our rheumatologists have adopted a more aggressive treatment approach to RA such that our RA population as a whole, as well as many individual patients, has shown dramatic clinical improvement. Additionally, about three-quarters of the ELDRA group had elderly-onset RA, which has reportedly had a milder course than younger onset disease. The study population has a very high level of education, which has repeatedly been found to correlate with better outcomes. We believe all these factors contribute to the impression of milder disease. However, as the data regarding joint replacements and fusions show, not all subjects have insignificant disease; our study subjects likely represent the clinical spectrum of RA who have been aggressively treated.

One might infer from our results that aggressive RA therapy is just as safe in ELDRA as in YRA patients. That the number of discontinued DMARD was similar only suggests this possibility. Similar safety is also implied by the fact that these rheumatologists do not avoid the use of any particular RA drug. Had use of a specific RA medication resulted in a clinically significant adverse event, it is likely physician practice would reflect such an outcome (i.e., that medication would not be used in the ELDRA population). This study did not specifically assess medication side effects or reasons for discontinuation, and therefore the conclusion that age bias should not exist for ELDRA patients cannot be made definitively.

Fleischmann, *et al*[2] performed a retrospective analysis of the combined results of 9 clinical trials of etanercept, in which the investigators compared the efficacy and safety outcomes of RA patients older and younger than age 65 years. The authors reported comparable ACR response rates and somewhat similar adverse event rates between the 2 groups. However, as these data were derived from formal clinical trials with strict selection criteria (i.e., not the general RA population) and only examined a single DMARD, the conclusions are also somewhat limited in their generalizability.

The implications of our results and those of Fleischmann's group are provocative. However, prospective

studies are necessary to further evaluate the safety and effectiveness of RA drugs in this population.

Maintaining mobility and activity among the elderly is clinically important for both physical and psychosocial health. Compounded comorbidity often results in less functional reserve, such that a particular medical condition that has minimal impact on a younger patient is likely to have greater health related consequences in an elderly individual with an underlying chronic disease. Thus, optimizing medical therapy for the elderly with active RA is imperative.

ACKNOWLEDGMENT

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