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ORIGINAL ARTICLE

Epidemiology and Treatment of New-Onset and Established Rheumatoid Arthritis in an Insured US Population

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Objective. **To investigate the epidemiology and treatment of rheumatoid arthritis (RA) in a population broadly representative of employed adults in the US, using a retrospective cohort design.**

Methods. **Incident and prevalent RA cohorts were defined from a sample of 4.66 million adults with complete followup data from the period of January 2005 through September 2008 in the Pharmetrics medical claims database. Demographics, comorbidity, and medical therapies were summarized using descriptive statistics.**

Results. **Median duration in the database was 5.7 years. Age- and sex-adjusted incidence in 2006 was 0.71 per 1,000 persons at risk (n = 3,992) and prevalence in 2005 was 0.63% (n = 30,530). Within 12 months after diagnosis, 65%, 64%, and 20% of the incident cohort had been prescribed corticosteroids, nonbiologic disease-modifying antirheumatic drugs (DMARDs), and tumor necrosis factor (TNF) inhibitors, respectively. Median time to first anti-TNF prescription was 6 months; 31% switched to a second drug and 15% to a third. An aggressive subcohort (11% of incident patients) received more DMARDs (83%) and TNF inhibitors (43%), and was more likely to switch. Twenty-eight percent of incident patients received only symptomatic therapy over a minimum of 1.75 years of followup; these patients were older with more comorbidities and contraindications to methotrexate.**

Conclusion. **In this insured population-based cohort, only two-thirds of newly diagnosed RA patients were prescribed a DMARD in year 1 and 28% received no antirheumatic therapy. Although limited by lack of clinical information and by left-censoring, administrative databases capture clinical practice and suggest that gaps exist in treatment options available to a significant number of patients.**

INTRODUCTION

Contemporary population-based epidemiologic studies of rheumatoid arthritis (RA) in the US are few, and with the exception of the prevalence estimates based on the National Health and Nutrition Examination Survey (1), ambulatory visits in the National Ambulatory Medical Care Survey (NAMCS), or National Hospital Ambulatory Medical Care surveys (2), are in either small, relatively homogeneous populations (3,4) or in women (5). Administrative databases provide another potential option because they contain systematically obtained information on defined populations that includes primary diagnosis, comorbidities, and treatments, albeit for purposes of generating a claim rather than for clinical care. Studies in databases such as Medicaid (6,7), Medicare (8–10), or insurance claims (11,12) have been used to describe treatment patterns in RA patients, and their findings are generally consistent with those from US clinical populations (13) or registries (14–17), but they have not been used for epidemiologic purposes. A concern has been the validity of diagnoses based on International Classification of Diseases, Ninth Revision (ICD-9) codes (18). Recent evaluations of algorithms for administrative data from Canadian (19) and US (20) investigators have indicated that, within carefully defined limits, claims data can provide valid information.

As noted above, administrative data can be used to understand treatment patterns for RA. Following publication of the American College of Rheumatology (ACR) recommendations in 2002 (21), subsequent observational studies that addressed uptake of nonbiologic DMARDs

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Significance & Innovations

- In this closed cohort of insured individuals with complete pharmacy and medical information, 15% of newly diagnosed rheumatoid arthritis (RA) patients did not visit a rheumatologist and 28% were not prescribed a disease-modifying antirheumatic drug during followup.
- One-quarter of incident patients were prescribed tumor necrosis factor inhibitors over a minimum of 1.75 years after diagnosis; there was a steady fall-off in their use after the initial prescription.
- Prevalence of RA was 0.63% and cumulative incidence was 0.07% in this geographically diverse US population.
- The study provides a baseline from the midpoint of the last decade to evaluate progress in implementing American College of Rheumatology guidelines for treatment of newly diagnosed RA in the US.

and/or anti–tumor necrosis factor (anti-TNF) therapies in US clinical populations (6–17) revealed considerable variability in how and whether patients were being treated with DMARDs. Below we extend these observations to newly diagnosed RA patients with complete followup over 3.75 years from a geographically disbursed subset of the US population. The analysis provides insight into how well contemporary treatment of RA reflects the guidelines and allows identification of gaps that may exist.

Our goals were to 1) determine the incidence and prevalence of RA, 2) characterize demographics and comorbidities in newly diagnosed patients, and 3) describe medical treatment patterns in newly diagnosed and established RA patients.

PATIENTS AND METHODS

Design and setting. We conducted a closed cohort study of incident and prevalent RA populations (Figure 1). In the US, most people under age 65 years are covered by fee-for-service, private sector health insurance plans. For payment, insurers require providers to generate a claim that encodes the primary and accompanying diagnoses, the service rendered, including prescription medications, and the relevant charges. Insurers have aggregated these claims into databases that capture all such encounters for all patients in a given health plan; these databases are available for research. Such databases may include patients ages ≥65 years, either because of continued employment or participation in private sector managed care Medicare plans; however, they are generally underrepresented because the great majority of persons age ≥65 years are covered by the government's Medicare plan. A global listing of health care databases that include claims databases can be found at the web site of the International Society of Pharmacoeconomics and Outcomes Research (http://www.ispor.org/DigestOfIntDB/CountryList.aspx).

Study population. The denominator for this study was defined as all patients age ≥18 years having medical information for at least the 3.75-year period from January 1, 2005 to September 30, 2008 (n = 4.66 of 52.1 million subjects) in a US health claims database (Pharmetrics Choice, IMS LifeLink: Health Plan Claims Database). Patients with RA and inflammatory polyarthritis (IP) were identified using ICD-9 codes (714.0–714.2 and 714.9, respectively).

Two mutually exclusive RA cohorts of interest were defined: a prevalence cohort and an incidence cohort. Within the incident cohort, "aggressive" and "nonaggressive" subcohorts were defined. The prevalent (established) cohort included patients with ≥2 outpatient (OP) or inpatient (InP) visits for RA, at least 2 being ≥30 days apart prior to January 1, 2006 or ≥1 visit with RA codes between January 1, 2006 and December 31, 2006, AND at least 1 OP visit for RA prior to January 1, 2006, again at least 30 days apart. The incident cohort included patients with RA codes in ≥2 separate OP/InP visits at least 30 days apart between January 1, 2006 and January 31, 2007 and no prior RA codes (previous polyarthritis code allowed). The aggressive incident subcohort consisted of incident RA patients with >8 OP/InP visits

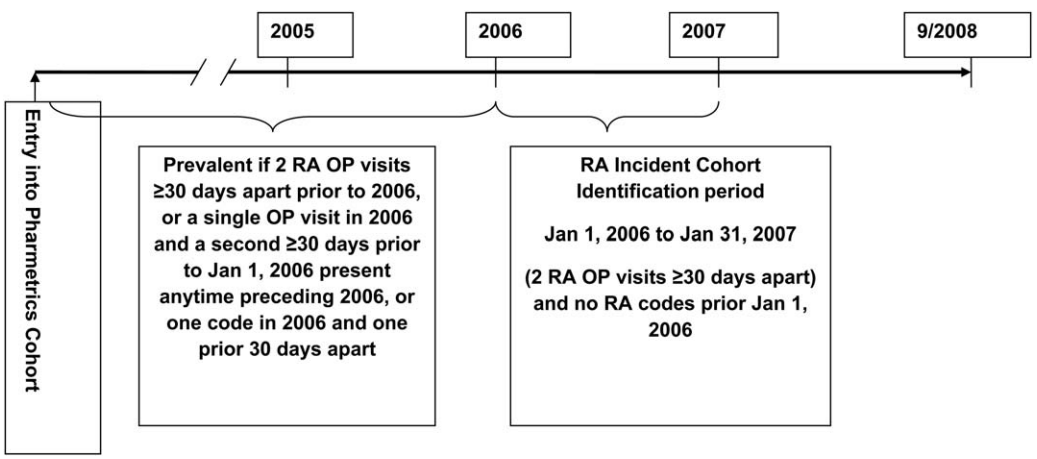

Figure 1. Sampling scheme for epidemiology and treatment of rheumatoid arthritis in US claims data. RA = rheumatoid arthritis; OP = outpatient.

involving RA in the 12 months following the initial diagnosis and no prior polyarthritis; the nonaggressive incident subcohort comprised the residual patients from the incident cohort who were not included in the aggressive subset. Two IP cohorts were defined using the same criteria for incident and prevalent RA. The sampling procedure is shown in Figure 1.

Variables. Comorbidities included cardiovascular, metabolic, infectious, psychological, and connective tissue disorders (codes are available from the authors). A single occurrence of the appropriate code as either an outpatient diagnosis or inpatient discharge diagnosis for the period up to January 1, 2007 was accepted as evidence of the disease for all except connective tissue diseases. For them, the same algorithm as for RA was applied, i.e., at least 2 separate OP/InP visits for the diagnosis that were at least 30 days apart.

Other comorbidities that captured possible contraindications to methotrexate (alcoholism, liver impairment, chronic kidney disease, immunodeficiency conditions, bone marrow failure, leukopenia, thrombocytopenia, or anemia; pregnancy and/or breastfeeding; and ascites or pleural effusions without drainage) were also assessed during the 12 months prior to and including the date of first diagnosis.

Medications potentially related to RA were identified in the database by either Generic Product Identifier codes or National Drug Codes or, if given as part of a procedure, as J-codes, and were associated with both a physician visit and a diagnostic code. The following categories were constructed: 1) nonbiologic DMARDs: methotrexate, leflunomide, sulfasalazine, minocycline, and hydroxychloroquine; 2) other nonbiologic DMARDS: azathioprine, cyclophosphamide, cyclosporine, mesalamine, penicillamine, and gold compounds; 3) TNF inhibitors: etanercept, infliximab, and adalimumab; 4) biologic agent, other: anakinra, rituximab, and abatacept; 5) corticosteroids: betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone; 6) narcotic analgesics: codeine, fentanyl, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, propoxyphene, propoxyphene napsylate, tramadol, butorphanol, pentazocine with naloxone, oxycodone with acetaminophen and propoxyphene (APAP), oxycodone with aspirin, aspirin with codeine, aspirin/caffeine/butalbit with codeine, dihydrocodeine compound, APAP with dydrocodone, propoxyphene compound, propoxyphene HCL with APAP, propoxyphene-n with APAP, and pentazocine with aspirin; 7) cyclooxygenase 2 inhibitors: celecoxib, rofecoxib, and valdecoxib; and 8) nonsteroidal antirheumatic drugs (NSAIDs): bromfenac, diclofenac, etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, and tolmetin.

For patients prescribed TNF-inhibitors, 3 patterns of failure were defined: primary discontinuations, primary switches, and secondary switches. Primary discontinuations were defined as patients who started an anti-TNF agent but had no further prescriptions over the course of at least 3 months of followup. Primary switches were considered to be patients who received ≥1 prescription for a given drug, followed by a change to a second agent; secondary switches were patients who were prescribed a third TNF inhibitor.

Statistical procedures. Disease rates are reported as cumulative incidence (persons newly diagnosed with RA/total persons at risk) and period prevalence (persons with RA prior to January 1, 2006); rates were age- and sex-adjusted to the estimated US population age ≥20 years in 2005, using the direct method. Kaplan-Meier curves were used to estimate the duration of use for TNF inhibitors.

RESULTS

Patient populations. There were 4.66 million participants fulfilling the entry criteria, 30,530 in the established cohort and 3,392 in the incident cohort. Median followup in the database was 5.7 years, and median time elapsed since diagnosis was 2.3 and 5.1 years in the incident and established cohorts, respectively. Complete pharmacy histories were available for 67% of patients in the incident cohort and 65% of the established cohort. Therefore, RA rates and comorbidities were estimated using the entire population, whereas treatment information was limited to the subset of 1,871 incident cohort patients and the 19,805 established cohort patients with complete medication histories.

Median age at first RA visit in the incident cohort was 56.0 years, but was 3 years lower in the aggressive subcohort (Table 1). Median and interquartile range (IQR) for duration of RA at last followup was 2.3 (2.1–2.5) years in the incident cohort and 5.1 (3.9–5.6) years in the established cohort.

Prevalence. Adjusted prevalence of RA at the end of 2005 was 0.63% overall, and 0.33% in males and 0.92% in females. One year later an additional 3,392 individuals were newly diagnosed with RA; in this static cohort, prevalence at the end of 2006 was therefore 0.73%. Prevalence of IP was 0.14%.

Incidence. Cumulative incidence of RA during 2006 was 0.73 (95% confidence interval [95% CI] 0.70–0.75) per 1,000 persons (1.00 and 0.44 in females and males, respectively). Age- and sex-specific rates are given in Figure 2 (truncated at the seventh decade due to small numbers in the older age groups). Eleven percent of incident cohort patients fell into the aggressive incident subcohort. IP incidence was 0.29 (95% CI 0.27–0.30) per 1,000 persons. IP occurred prior to the RA diagnosis in 11.5% of incident cohort patients (5% occurred prior to 2006 and another 6.5% during 2006); the overlap between prevalent RA and prevalent IP was just under 10%.

Comorbidities. Cardiovascular, metabolic, pulmonary, and neoplastic comorbidities based on at least 1 code and 1 visit prior to 2006 are presented in Table 1. The ICD-9 code for fatigue was common, and approximately 14% of each cohort had at least 1 prior visit for osteoarthritis. Prevalence of other connective tissue diseases, based on a stricter criterion of having 2 separate codes at least 30 days apart prior to 2006, was 8% in the incident cohort

Table 1. Demographics, physician visits, followup times and comorbidities in the 12 months after diagnosis for the incident and establish RA cohorts and the incident subcohorts*

	Incident RA (n = 3,392)	Aggressive incident RA (n = 385)†	Non-aggressive incident RA (n = 3,007)†	Established RA (n = 30,530)
Age in 2005, median (IQR) years	56.0 (47.0–66.0)	53.0 (45.0–62.0)	56.0 (48.0–66.0)	57.0 (49.0–66.0)
Age at first RA visit ever, median (IQR) years	57.0 (48.0–67.0)	54.0 (46.0–63.0)	57.0 (49.0–67.0)	55.0 (47.0–64.0)
Male	28.7	26.5	29.0	25.9
Female	71.3	73.5	71.0	74.1
Followup in database, median (IQR) years	5.7 (4.9–5.7)	5.7 (4.9–5.7)	5.7 (4.9–5.7)	5.7 (5.4–5.7)
Physician OP/IP visits for RA in 12 months after first RA diagnosis				
1–4 visits	46.9	0	52.8	49.9
5–8 visits	29.5	0	33.2	27.3
>8 visits	23.5‡	100	14.0‡	22.8
Proportion with polyarthritis (714.9) prior to first RA diagnosis	16.6	10.4§	17.4	6.7
Comorbidities through end of 2006¶				
Diabetes mellitus, any	20.7	20.3	20.8	20.0
Any cardiovascular disease	22.6	17.7	23.2	22.0
Any non–skin cancer	2.5	1.3	2.7	2.5
Osteoarthritis	14.4	12.5	14.6	13.6
Psoriatic arthritis	5.6	2.9	6.0	6.2
Spondylarthropathy	6.7	5.2	6.9	6.1
Connective tissue disorders#	7.9	3.6	8.5	9.7
Unspecified diffuse connective tissue disorders	2.5	1.8	2.6	3.0
Chronic anemia	22.1	25.2	21.7	24.2
Anxiety	17.5	14.5	17.9	16.3
Depression	18.0	16.6	18.1	17.9

* Values are the percentage unless indicated otherwise. RA = rheumatoid arthritis; IQR = interquartile range; OP = outpatient; IP = inflammatory polyarthritis.
† "Aggressive" is defined as >8 visits, including hospitalizations in the first 12 months after first diagnostic code and no prior polyarthritis code; non-aggressive is what is left after subtracting aggressive from the incident cohort.
‡ Incident cohort includes both the aggressive, all of which had >8 visits, and the nonaggressive, with >8 visits who had a prior IP diagnosis (exclusion criterion for aggressive patients).
§ Polyarthritis codes occurred during 2006 between first and second occurrence of RA code.
¶ Proportion of patients with a given comorbidity based on a single occurrence of the relevant code.
# Diagnosis based on the requirement of 2 visits at least 30 days apart.

and 9.7% in the prevalence cohort. The greatest overlaps between connective tissue diseases and RA were for systemic lupus erythematosus (approximately 4%) and sicca syndrome (approximately 2%). The distribution of comorbidities in the established cohort was similar to the incident cohort.

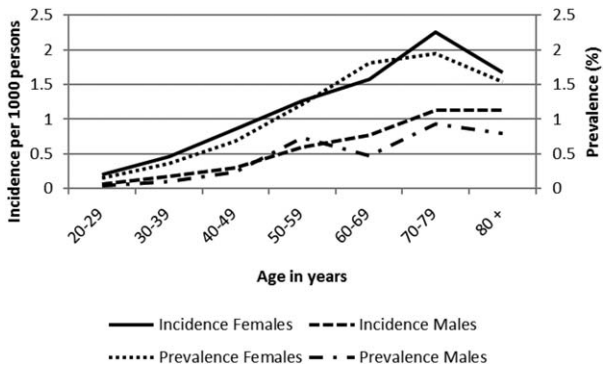

Figure 2. Age and sex incidence rates per 1,000 persons for all rheumatoid arthritis (calendar year 2006) and prevalence (%) for all rheumatoid arthritis at the end of 2005, age truncated in the seventh decade due to disproportionately smaller populations at risk in the elderly.

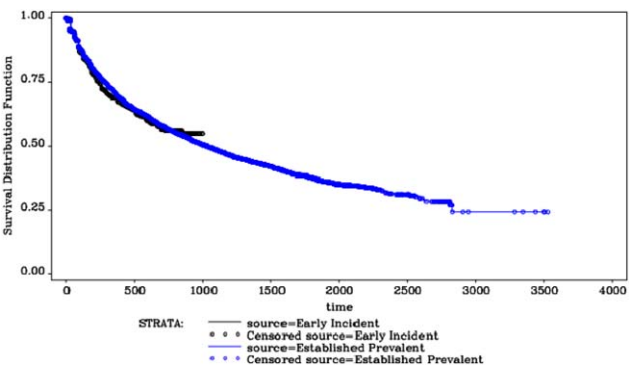

Figure 3. Time on biologic therapy in newly diagnosed and prevalent patients. Data provided by Pharmetrics Database.

Table 2. RA treatment patterns for incident cohort and subcohorts during the first 12 months after diagnosis, and in the established cohort during the 12 months after the first RA visit in the database, subset of patients with complete medication histories*

	Incident RA (n = 2,136)	Aggressive incident RA (n = 265)†	Nonaggressive incident RA (n = 1,871)	Established RA (n = 19,805)†
A. With a methotrexate prescription prior to January 1, 2006				
Methotrexate	6.7	2.6	7.3	47.8
B. With ≥1 prescription in 12 months after first diagnosis date				
Selected DMARDs, any	64.0	83.4	62.6	55.1
Methotrexate	45.8	76.2	41.5	41.7
Leflunomide	6.0	13.6	5.0	7.3
Cyclosporine	0.3	0.0	0.3	0.3
Sulfasalazine	7.5	9.1	7.3	8.1
Mesalamine	0.9	1.1	0.9	0.6
Hydroxychloroquine	25.8	26.4	25.7	24.1
Biologic anti-TNF, any	20.4	43.4	17.2	22.1
Etanercept	10.8	23.4	9.0	13.1
Infliximab	5.8	10.2	5.1	6.9
Adalimumab	6.4	14.7	5.2	3.8
Biologic, other, any	0.6	1.5	0.4	0.7
Anakinra	0.1	0.4	0.1	0.6
Rituximab	0.2	0.8	0.2	0.1
Abatacept	0.2	0.4	0.2	0.0
Corticosteroids	65.2	83.4	62.6	55.1
Other medication				
NSAIDs	43.5	46.8	43.1	37.0
COX-2 inhibitors	10.5	15.1	9.9	24.9
Narcotic analgesics	47.6	56.2	46.3	40.0
At least 1 biologic or nonbiologic DMARD	67.9	89.4	64.8	67.5
At least 1 biologic or nonbiologic DMARD and/or steroids	82.0	95.1	80.2	80.0
At least 1 biologic or nonbiologic DMARD or steroids or pain medication	98.3	99.2	98.1	98.5
C. Anti-TNF usage over total followup				
≥1 TNF inhibitor prescription	27.7	54.0	24.0	35.0
Primary discontinuation rate	3.4	0	4.7	2.2
Primary switch rate	31.0	28.4	31.6	25.6
Secondary switch rate	15.3	15.0	15.5	20.1

* Values are the percentage. RA = rheumatoid arthritis; DMARDs = disease-modifying antirheumatic drugs; anti-TNF = anti–tumor necrosis factor; NSAIDs = nonsteroidal antirheumatic drugs; COX-2 = cyclooxygenase 2.
† Therapies in established RA group were subject to left-censoring; therefore, true value may have been greater.

Providers. In the 12 months after diagnosis, 62% of the incident cohort consulted a rheumatologist and 83% of the aggressive subcohort did so. Over the entire followup period, 15% of the incident cohort was followed exclusively by nonrheumatologists, including general practitioners, internists, and physicians of other or unknown specialty. In the calendar year 2006, 24% of the established cohort had no recorded OP visit; of those who did, two-thirds saw a rheumatologist.

Treatment patterns. Sixty-four percent of the incident cohort was prescribed a nonbiologic DMARD in year 1. Methotrexate was the most frequent (45% in year 1), followed by hydroxychloroquine, leflunomide, and sulfasalazine (Table 2). Median (IQR) time to first methotrexate prescription was 1 month (0–10). Methotrexate was started as monotherapy in 49%, as monotherapy with a subsequent add-on DMARD in 18%, as delayed add-on to another DMARD, and as combination therapy in 4% of treated patients. Based on prescription refills, the proportion of patients continuing methotrexate treatment declined to 70% within 6 months and to 62% after 12 months. In the incident cohort, 18% of patients had a potential contraindication to methotrexate based on the 7 conditions in the Methods, and 9.2% had a code for anemia occurring in the 30 days prior to diagnosis. DMARD use was greater in the aggressive incident subcohort than in the non–aggressive subcohort.

TNF inhibitors were prescribed to 20% of the incident cohort in the first 12 months after diagnosis and to an

Table 3. Selected characteristics of treatment segments defined over a 2-year period in an incident RA cohort newly diagnosed in 2006 (n = 2,136)*

	Both anti-TNF and DMARD (n = 489)	DMARD only (n = 963)	Anti-TNF only (n = 76)	No anti-TNF or DMARD (n = 608)
A. Demographic characteristics, % of total	23	45	4	28
Age at first RA diagnosis, mean (median) years	49.5 (50.0)	51.7 (52.0)	47.7 (48.5)	54.3 (54.0)
Duration of followup in database, mean (median) years	5.4 (5.6)	6.4 (5.7)	5.3 (5.7)	5.4 (5.7)
Duration of RA, mean (median) years	2.3 (2.3)	2.3 (2.3)	2.3 (2.3)	2.3 (2.3)
Female	76.1	72.9	59.2	69.6
Number of total visits for RA, mean (median)	9.8 (9.0)	6.4 (6.0)	6.7 (5.5)	4.0 (3.0)
Number of generalist visits/RA, mean (median)	2.3 (1.0)	2.2 (1.0)	2.7 (2.0)	2.2 (2.0)
Number of rheumatologist visits for RA, mean (median)	7.1 (6.0)	4.8 (4.0)	4.6 (4.0)	3.3 (2.0)
Aggressive subcohort	26.0	10.8	14.5	3.8
B. Comorbidities prior to 2006†				
Diabetes mellitus, type 1 or type 2	16.8	13.5	15.8	24.8
Cardiovascular disease	9.8	13.2	15.8	21.2
Cancer	0.6	0.9	0.0	2.3
Osteoarthritis	12.5	10.9	11.8	13.8
Psoriatic arthritis	10.6	3.7	28.9	2.8
Spondylarthropathy	10.0	6.6	17.1	5.1
Connective tissue disorders	12.7	20.9	14.5	12.5
Unspecified diffuse connective tissue disease	4.5	9.0	3.9	4.1
C. Methotrexate contraindications				
Alcoholism	0.6	1.1	1.3	0.6
Liver impairment (without 7904, 7948)	4.5	4.9	3.9	9.2
Chronic kidney disease	1.4	1.2	1.3	1.2
Immunodeficiency conditions	1.4	1.2	2.6	2.5
Bone marrow failure, leukopenia, thrombocytopenia, or anemia	8.4	5.9	7.9	13.3
Pregnancy and lactating women	3.1	0.9	1.3	1.6
Ascites or pleural effusions without drainage	1.0	0.9	1.3	0.8
Any 1 of the 7 conditions above	18.6	14.1	17.1	23.2
D. Nonspecific measurements 30 days prior to and including date of diagnosis (ICD-9 code)				
Anemia unspecified (2859)	8.4	7.5	7.9	12.7
Nonspecific abnormal liver scan (7948)	2.0	1.7	1.3	2.5
Nonspecific elevation of transaminase levels or LDH (7904)	1.6	1.6	0.0	2.0
E. Other treatments given at least once after diagnosis				
Biologic agent, other	5.7	0.9	1.3	0.7
NSAIDs	56.9	56.2	46.1	40.0
Narcotic analgesics	67.9	62.5	46.1	53.1
COX-2 inhibitors	16.0	13.3	11.8	11.8
Corticosteroids	91.4	79.1	56.6	51.6
No corticosteroids, COX-2, narcotics or other pain meds	1.0	5.0	23.7	0.0
Arthrocentesis, year 1	34.4	26.9	21.1	20.4

* Values are the percentage unless indicated otherwise. RA = rheumatoid arthritis; anti-TNF = anti–tumor necrosis factor; DMARD = disease-modifying antirheumatic drug; ICD-9 = International Classification of Diseases, Ninth Revision; LDH = lactate dehydrogenase; NSAIDs = nonsteroidal antirheumatic drugs; COX-2 = cyclooxygenase 2.
† Comorbidity rates differ from Table 1, which included all patients; whereas this Table is for the subset of patients with complete pharmacy records.

additional 7% by the end of the first 2 years; corresponding figures were 43% and 9%, respectively, in the aggressive incident subcohort. Median time (IQR) to first prescription was 6 (2–13) and 5 (3–11) months for each group, respectively. The most commonly prescribed TNF inhibitor initially was etanercept, followed by adalimumab and infliximab. Primary discontinuations and primary/secondary switch rates are presented in Table 2. Kaplan-Meier estimates of the duration of anti-TNF use in the incident cohort provided discontinuation rates of 0%, 18%, and 31% at 6, 12, and 18 months, respectively; equivalent figures in the established cohort were 0%, 17%, and 36% based on earliest start date available (left-censoring possible). Overall, the proportion of incident and established patients who received a DMARD was similar (67%).

After 2 years of followup in the incident cohort, 4 RA treatment patient segments were identified: DMARDs alone, DMARDs and subsequent TNF inhibitors, TNF inhibitors

alone, and no antirheumatic treatment (Table 3). The majority of patients fell into either the first (45%) or the second (23%) segments. The TNF inhibitor monotherapy group was small (<4%, n = 76) and median age at diagnosis was 4 years younger than the DMARDs group, which was 2 years below the combination group, and included more men. Patients receiving anti-TNFs alone often had comorbidities that also respond to anti-TNF agents (psoriatic arthritis [29%] and spondyloarthropathy [17%]) and the highest use of analgesics (68%), corticosteroids (91%), NSAIDs (57%), and other biologic agents as monotherapy (5.7%). By contrast, the no therapy group had the highest median age at diagnosis (54.0 years), the greatest co-occurrence of diabetes mellitus (24.8%), heart disease (22.0%), and anemia (34.4%), the lowest proportion of at least 1 arthrocentesis procedure in year 1 (20.4%), and the fewest number of physician visits to any provider (median 3.0) or to a rheumatologist (median 2.0) for RA in year 1. Although this group received no particular RA therapy, all received symptomatic treatment, the most common being narcotic analgesics (52%), corticosteroids (52%), and NSAIDs (40%).

DISCUSSION

In this US population-based study, 4 years after publication of ACR treatment guidelines in 2002, more than one-quarter of newly diagnosed RA patients did not receive DMARD therapy for a minimum of 1.75 years followup and, although one-fifth were prescribed biologic agents within 12 months, there was extensive switching among them, as well as a relatively rapid decline over time in the proportion of patients who remained on therapy. This population was arguably underserved, because 38% of this inception cohort did not see a rheumatologist in year 1 and 15% never saw one over a median of 2.3 years of followup. Incidence of RA was slightly higher than and prevalence was very similar to rates from another population-based study in the US (3). Incidence was highest in the age group 70–79 years, which could reflect a delay in diagnosis or in coding, or the non-representativeness of the Medicare-aged population covered by this database. Explanations for the apparent undertreatment of patients might include care by a physician who either was not aware of the guidelines or disagreed with them, or had decided that the patient was either too frail, the patient's disease was too mild, or the patient had too many contraindications for effective therapy. Also, the patient may have preferred to avoid treatment because of cost or side-effects, or the original RA diagnosis turned out to be something else.

In an assessment of DMARD treatment in US fee-for-service Medicare patients, 24% of whom had not been prescribed a DMARD, medical reasons such as remission or medical contraindication were the most common explanations for nontreatment (22). Because claims data do not include any measure of disease severity, there is no direct way to assess the proportion of mild patients, although a significant proportion of newly diagnosed RA is self-limiting (23). In comparison to patients who received both DMARDs and biologic treatment, untreated patients were older (median 54 versus 50 years), more likely to have had serious comorbidities, and less likely to have received symptomatic therapy in year 1. Although this cohort had fewer mean physician visits than the others, they averaged 2 per year and a median of 2 visits to a rheumatologist over followup, which suggests there was ample opportunity to initiate RA therapy.

This pattern of apparent undertreatment is consistent with other US population-based cohorts with DMARD treatment rates in the range of 63–90% (6,10,12,24,25), and may simply reflect the proportion of patients with mild disease in population-based cohorts, or else personal preference or economic or educational barriers. An analysis of DMARD starters in the latter registry identified young age, Hispanic ethnicity, shorter duration of disease, and use of oral corticosteroids as predictors of initiating DMARD (25). In Medicare cohorts, DMARD usage declined with age (8,9) and number of comorbidities (8), and DMARD initiation was associated with a visit to a rheumatologist (12).

A possible methodologic explanation for the apparent undertreatment of RA is that the incident cohort may have included false positives, either due to misdiagnosis or coding errors. In validation studies of the use of ICD-9 codes to identify RA patients in databases, sensitivity is fairly high, specificity is lower, and positive predictive values (PPVs) vary dramatically (19,20). For example, in the Mayo Clinic electronic database, using a single occurrence of the ICD-9 code, the ACR 1987 criteria for diagnosis of RA, and a rheumatologist's review as a gold standard, the sensitivity was 89% and the specificity was 74%, but the PPV was 57% in prevalent patients (26). Kim et al (20) studied 3 algorithms using multiple codes (2 claims for RA, 3 claims for RA, and 2 claims for an RA visit to a rheumatologist at least 7 days apart), and used rheumatologist opinion and 1987 ACR criteria as the gold standard, and found PPVs to be between 33% and 67%, the lower values reflecting the 1987 ACR criteria for RA as gold standard.

Widdifield et al (19) evaluated sensitivity and specificity of ICD-9 codes against a validation sample of 7,500 randomly selected patient records using various combinations of OP and/or InP and/or specialist visits against a gold standard of a rheumatologist's diagnosis. Their analysis gave PPVs as low as 42% and as high as 80% in adults and implied post-test prevalence rates from 0.9% to 1.8%. A single hospital visit or 3 OP visits, in which ≥1 was with a specialist over 2 years, gave a sensitivity, specificity, and PPV of 78%, 100%, and 78%, respectively, with a post-test prevalence of 0.9%, which was the actual prevalence in their sample. The algorithm used herein was closest to theirs, based on 2 visits within a 12-month period (but no specifications on time between visits), which gave a PPV of 46% and an implied prevalence of 1.7% (versus our figure of 0.73% at the end of 2006). We cannot account for this discrepancy other than to assume that the requirement of at least 30 days between visits may have improved sensitivity.

The majority of patients who received TNF inhibitors in this study did so after a trial of DMARDs, and the one-quarter of the incident cohort patients who were prescribed therapy by the end of year 2 is consistent with other studies from that period (6,7,12,16,17,27). Although supporting

clinical information is not available in a claims database, the treatment pattern in the aggressive subcohort may anticipate how the 2008 ACR criteria and subsequent recommendations (28,29) would be reflected in newly diagnosed RA patients: greater use of DMARDs (83%), rapid time to first prescription (median [IQR] 1 month [0–4]), use of steroids (83%), and rapid addition of a TNF inhibitor (43% by end of year 1, median time to start 6 months).

Biologic switch rates over >2 years of followup in this study (31%) were similar to European registries (30–32). Switching could be due to cost of the drug, patient preference, adverse events, intolerance, or inefficacy. The absence of clinical data in this study prohibits any conclusions about the relative importance of each, but a review of experience in 8 registries and cohorts suggests that by 6 months after therapy between 4% and 23% of patients who started etanercept or infliximab had withdrawn due to lack of efficacy, as did between 3% and 16% of patients starting adalimumab (33). Although withdrawal rates for adverse events were lower, they ranged between 2% and 16%. These data are consistent with the 18% 12-month withdrawal rate observed in the current study and the 18% 2-year withdrawal rate reported by the Danish Registry for Biologic Therapies in Rheumatology (DANBIO) Registry (34), and cumulatively suggest that TNF inhibitors, over time, provide suboptimal therapy for a significant fraction of patients.

Previously reported population-based estimates of RA incidence and prevalence vary considerably: 0.1–0.5 per 1,000 person-years for incidence and 0.18–0.85% for prevalence, depending on the population and method of study (35). Our prevalence rate (0.63%) was lower than in other cohorts, such as the Olmsted County cohort in the US (0.72%) or the Norfolk Registry in the UK (0.85%) (3,36), but close to the 0.68% derived from the NAMCS analysis of physician visits (2). A possible explanation is that these 2 studies were able to capture a lifetime history of RA in their prevalence estimates, whereas a claims database study is severely constrained by left-censoring, resulting in the lack of a complete medical history. In contrast to prevalence, the incidence rate in this study was greater (0.7 per 1,000 person-years) than those reported by the Mayo Clinic (0.41 per 1,000 person-years) or the UK Norfolk Arthritis Registry (0.25 per 1,000 person-years to approximately 0.39 per 1,000 person-years) (3,37,38), but this may be due to the mixing of true incident with some prevalent patients who were relapsing, but whose medical history was truncated due to left-censoring.

Despite these limitations, administrative claims databases provide insight into the daily practice of clinical medicine for any disease or condition that can be defined using an ICD code. Claims data can provide a population-based overview of all providers, all therapies, all reported comorbidities, and all disease-related reimbursable encounters, as well as total costs (both direct and out-of-pocket), therefore providing a comprehensive window into the overall burden of illness associated with RA in the US. The major disadvantage is the lack of any clinical information. The second disadvantage is that the data are censored; however, both left-censoring (no history prior to entry) and right-censoring (incomplete followup due to patients switching medical coverage plans) are issues shared by all cohort studies, as is the question of generalizability (39). With respect to the latter, when compared to the US population age ≥20 years, the Pharmetrics Choice database overrepresented people of working age (91% versus 83%), people resident in the Northeast (27% versus 19%) and Midwest (38% versus 22%), and underrepresented persons age ≥65 years (2% ≥66 years versus 12%). There were no sex differences. The age difference was further exaggerated in the subset of Pharmetrics participants with complete medication histories, most likely because the database is restricted to persons who are employed and are enrolled in commercial PPO plans.

In conclusion, this US population-based study characterizes RA patients in terms of incidence, prevalence, clinically relevant subpopulations, and treatment patterns at the middle of the last decade. Reasons for the lack of antirheumatic treatment in a significant portion of patients, despite adequate insurance coverage, need to be clarified, since this pattern has been reported elsewhere and may indicate a gap in treatment options. The switching among TNF inhibitors and the decline in use over time suggests a second gap. Although TNF inhibitors are effective in the RA patient population refractory to methotrexate, the advent of newer RA treatments with different mechanisms of action, such as abatacept, rituximab, tocilizumab, and tofacitinib, present an area for future investigation.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Crane had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Crane, Kurrasch, Manson, Chang.
Acquisition of data. Juneja.
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ROLE OF THE STUDY SPONSOR

Authors were employees of GlaxoSmithKline at the time this research was conducted. The design, data collection, analysis and interpretation of the data were based on the authors' best judgement as to scientific merit. The decision to submit the manuscript for publication was made by all authors. The manuscript underwent standard GlaxoSmithKline review and approval process prior to submission.

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