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ORIGINAL RESEARCH

Treatment Patterns of Newly Diagnosed Rheumatoid Arthritis Patients from a Commercially Insured Population

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ABSTRACT

Introduction: To describe treatment patterns in newly diagnosed rheumatoid arthritis (RA) patients in a large, nationally representative managed-care database.

Methods: Newly diagnosed RA patients were identified from 07/01/2006–08/31/2014. Patients had ≥ 1 RA diagnosis by a rheumatologist, or ≥ 2 non-rheumatologist RA diagnoses ≥ 30 days apart, or RA diagnosis followed by a disease-modifying antirheumatic drug (DMARD) prescription fill within 1 year. Patients were ≥ 18 years old at index (earliest date fulfilling diagnostic criteria) and had ≥ 6 and 12 months of pre- and post-index health plan enrollment, respectively. Patterns of DMARD treatment, including conventional synthetic DMARDs (csDMARD), tumor necrosis factor inhibitors (TNFi), non-TNFi, and Janus kinase inhibitors (JAKi), were captured during follow-up.

Results: Of the 63,101 RA patients identified, 73% were female; mean age was 57 years. During an average of 3.5 ± 2.1 years of follow-up, 45% of patients never received a DMARD, 52% received a csDMARD (94 ± 298 mean $\pm$ SD days from index), 16% a TNFi (315 ± 448 days), 4% a non-TNFi (757 ± 660 days), and $< 1\%$ a JAKi. Among DMARD recipients, the most common treatment patterns were: receiving csDMARDs only (68%), adding a TNFi as second-line therapy after initiation of a csDMARD (12%), and receiving only a TNFi (6%) during follow-up. Among those not on DMARDs, the all-cause usage of an opioid was 56% and 19% had chronic opioid use (≥ 180 days supplied).

Conclusions: Despite American College of Rheumatology recommendations for DMARD treatment of RA, nearly half of newly diagnosed RA patients received no DMARD therapy during follow-up. These data identify a treatment gap in RA management.

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INTRODUCTION

Rheumatoid arthritis (RA) affects an estimated 1.3 million adults in the United States (US), is twice as prevalent in women as in men, and is associated with a range of signs and symptoms that include pain, fatigue, and joint stiffness [1–3]. Because of its debilitating symptoms, RA strains the resources of healthcare systems, exacts severe economic burdens on patients and their families, and diminishes quality of life along with patients' ability to work and function normally [4, 5]. Inflammation caused by the disease can lead to cartilage damage and destruction of the joints [6]. RA patients may have multiple comorbidities and psychosocial impairments including cardiovascular disease, osteoporosis, interstitial lung disease, infections, malignancies, fatigue, depression, and cognitive dysfunction, among others [7]. Thus, it is vital that RA disease activity is controlled to lessen the disease-related burden on patients' personal lives and the healthcare system as a whole.

The American College of Rheumatology (ACR) RA treatment recommendations specify the use of conventional, synthetic disease-modifying antirheumatic drugs (csDMARDs) as first-line therapy for newly diagnosed RA patients to minimize or prevent progressive damage to joints and improve long-term outcomes [8, 9]. Currently, methotrexate, hydroxychloroquine, sulfasalazine, or other csDMARDs are well established as first-line DMARD treatments for RA; however, multiple therapeutic options are now available beyond csDMARDs for patients who fail to achieve their treatment goal on these agents [6, 8, 10], including biologic therapies and a Janus kinase inhibitor (JAKi) [11–13].

Despite the increasing availability of therapeutic options for RA management, not all patients receive recommended therapy. Physician-perceived barriers to therapy include cost to patient and insurance/formulary coverage [14]. Patient factors that may influence therapy choice include the fear of side effects and a belief in adequate disease control despite many patients exhibiting discordant moderate or higher RA disease activity scores [15].

Attainment of remission or low disease activity remains challenging for many patients [16]. The management of RA has implications on the overall cost and quality of care for patients, providers, and payers [6, 10, 17–19].

The availability of recent population-based estimates of RA treatment patterns is limited. Such information would be of interest to parties involved in the management of this disease. This study aimed to address this knowledge gap by examining treatment patterns within a population of newly diagnosed RA patients using a large, nationally representative managed-care database.

METHODS

Study Design and Data Source

This observational cohort study queried medical and prescription claims from the HealthCore Integrated Research Database (HIRD)^SM, a repository of longitudinal claims data for approximately 40 million health plan enrollees across the US. The study population of interest was newly diagnosed RA patients. The study cohort consisted of patients identified during the period from July 1, 2006 through August 31, 2014 based on a combination of claims-based algorithm [20, 21]. The index date was defined as the earliest date on which a patient fulfilled one of the three algorithm criteria. Study data were handled in compliance with all applicable Health Insurance Portability and Accountability Act (HIPAA) rules. Patient anonymity and confidentiality were preserved with data de-identification throughout. Investigational Review Board (IRB) informed consent requirements were waived for this non-experimental study, which was conducted under the research exception provisions of the Privacy Rule, 45 CFR 164.514(e).

Inclusion/Exclusion Criteria

Study patients were ≥ 18 years on their index date and had continuous enrollment with both medical and pharmacy benefits during the

6-month period preceding the index date and for ≥ 1 year post-index. To be considered newly diagnosed patients, no RA diagnoses were allowed during the 6-month pre-index period. Patients meeting any one of three claims-based criteria were included: (1) presence of ≥ 1 medical claim for an RA diagnosis (ICD-9 714.0x, 714.1x, or 714.2x) by a rheumatologist; (2) ≥ 2 medical claims with an RA diagnosis by a non-rheumatologist occurring at least 30 days apart; or, (3) presence of ≥ 1 medical claim with an RA diagnosis occurring concurrently with or followed by a medical or pharmacy claim for any DMARD therapy within 1 year. Patients were followed beyond 1 year until they reached the end of the study period, left the health plan, or died, whichever occurred first. Patients with ≥ 1 claim of a cancer diagnosis (ICD-9 code 140.xx–209.3x, 230.xx–234.xx) during the 6-month pre-index period were excluded from the study.

Treatment Pattern Definitions

Patterns of DMARD treatment—including csDMARDs, biologic tumor necrosis factor inhibitors (TNFi; etanercept, adalimumab, infliximab, certolizumab, and golimumab), biologic non-TNFi (abatacept, rituximab, tocilizumab, anakinra), and JAKi (tofacitinib)—were assessed during follow-up. Additionally, use of prescription pain medications (opioids, nonsteroidal anti-inflammatory drugs [NSAIDs], muscle relaxants, and anticonvulsants) and steroids (oral and injectable glucocorticoids) were examined. All-cause chronic opioid use was defined as receiving ≥ 180 days supply of opioid medication during the follow-up period. Discontinuation of DMARD treatment was considered as the absence of a claim for a DMARD within 90 days after the last day supplied of the most recent medication claim. The discontinuation date was defined as the last medication claim date plus the days supplied for that claim. Switching was defined as the filling of a DMARD class that was different from any medication in the current regimen or most recent prior medication while not continuing the original therapy; stopping and restarting the same medication was not considered a switch.

Add-on therapy included the filling of a second DMARD class while maintaining continuous therapy with a previously prescribed DMARD. A maximum of three treatment changes (adding on or switching therapy) were captured for each patient, resulting in the capture of up to four lines of DMARD treatment. Medication dosage was not captured in this study.

Two sensitivity analyses were conducted: (1) limiting the analysis to patients identified during January 1, 2010 through August 31, 2014 to account for the potential evolution in therapeutic management and treatment recommendations in recent years, and (2) requiring patients to have three distinct RA diagnosis on distinct dates when the diagnostic workups or tests (e.g., imaging of joint, laboratory test for C-reactive protein, synovial fluid analysis rheumatoid factor, cyclic citrullinated peptide, erythrocyte sedimentation rate) used for diagnosing/ruling out RA were not included, AND visited a rheumatologist at time of first diagnosis.

Baseline Characteristics

Prespecified comorbid conditions were defined as the presence of ≥ 1 diagnosis code for the condition of interest during the 6-month pre-index period. The Quan–Charlson Comorbidity Index (QCI) was calculated to quantify the burden of comorbid disease in this population [22]. The specialty of the physician associated with the RA diagnosis was identified on the index date medical claim. If physician information was not available on the index date, the claim closest to the index date (either pre- or post-index) with a diagnosis for RA was used to determine diagnosing specialty.

Statistical Analysis

This single-cohort study of RA patients was descriptive in nature, and treatment patterns were analyzed within the entire cohort with no comparison group. Descriptive statistics (means, standard deviations, medians, frequencies, and percentages) were reported for each outcome of interest. All analyses were conducted using SAS Enterprise Guide v7.1 (Cary, NC, USA).
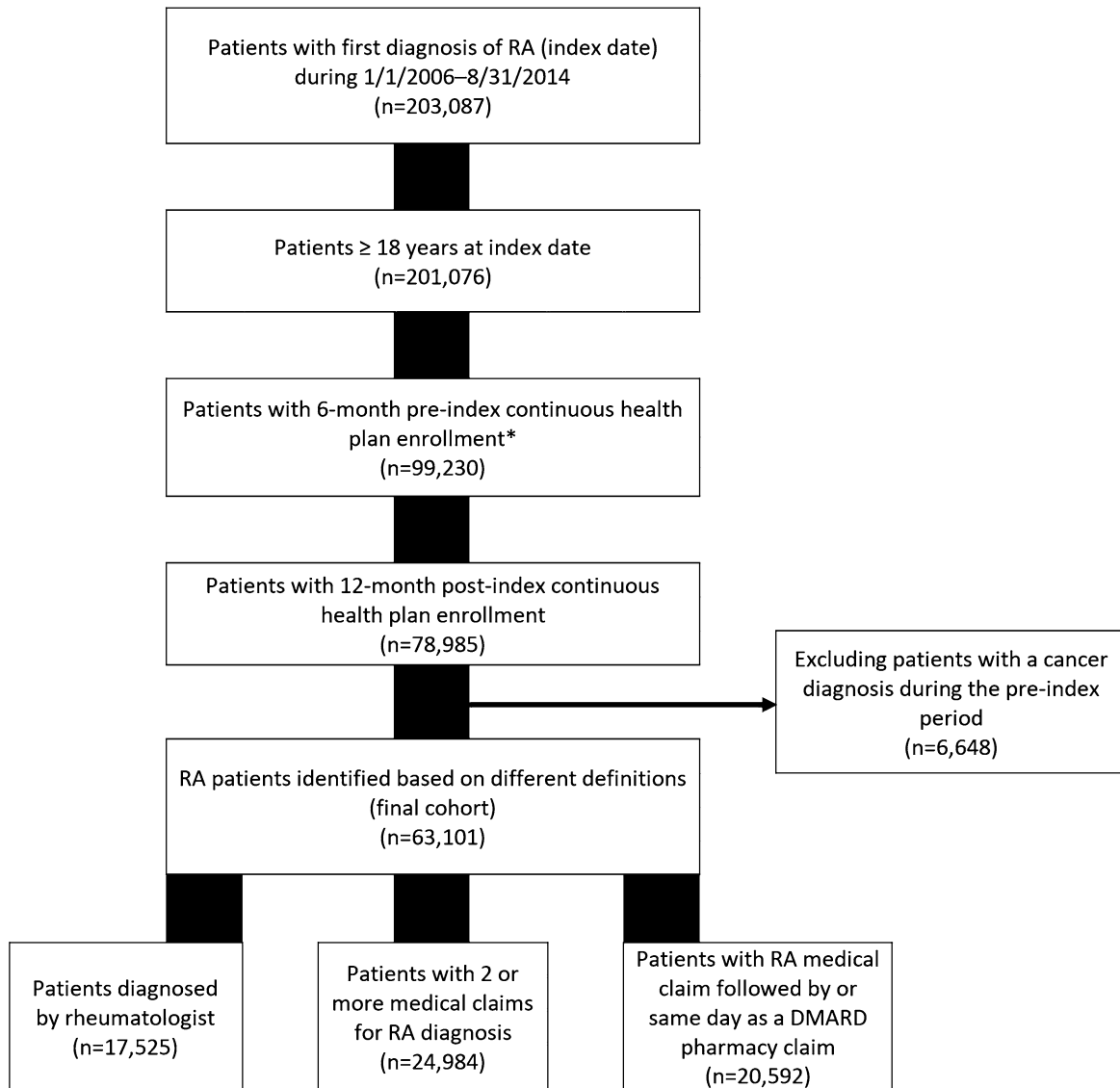
Fig. 1 Patient selection for the study and the number of patients included in the final analytic cohort. *By requiring 6 months pre-index criteria the identification period of patients effectively becomes 7/1/2006 through 8/31/2014

RESULTS

Demographics and Baseline Data

After applying inclusion and exclusion criteria (Fig. 1), there were 63,101 RA patients with mean ± SD age of 57 ± 15.6 years, and 72.7% were female (Table 1). Most patients were enrolled in preferred provider organization (PPO) health plans (72.5%), and 27.8% had Medicare Advantage or Medicare Supplemental plus Part D coverage. Nearly half of the study population (44.2%) was diagnosed or treated by a rheumatologist at index. Hypertension (40.5%), dyslipidemia (34.0%), and

Table 1 Baseline patient characteristics ($N = 63,101$)

Characteristic	Mean±SD or n (%)
Female	45,854 (72.7)
Age at index (years)	57.0±15.6
Geographic region	
Northeast	12,181 (19.3)
Midwest	18,111 (28.7)
South	16,580 (26.3)
West	13,467 (21.3)
Unknown	2,762 (4.4)
Health plan type	
HMO	14,002 (22.2)
PPO	45,775 (72.5)
CDHP	3324 (5.3)
Medicare Advantage, Supplemental and Part D	17,543 (27.8)
Treating/prescribing physician specialty	
Rheumatologist	27,922 (44.2)
Internal medicine	7171 (11.4)
Family medicine/general practice	6429 (10.2)
Unknown	2687 (4.3)
All others	18,892 (29.9)
QCI	0.9±1.3
QCI categories	
0	29,870 (47.3)
1–2	26,829 (42.5)
> 3	6402 (10.1)
Comorbid conditions[a]	
Hypertension	25,525 (40.5)
Dyslipidemia	21,464 (34.0)
Osteoarthritis	19,642 (31.1)
Mental illness	12,903 (20.4)
Type 2 diabetes	9075 (14.4)
Unspecific arthritis	8919 (14.1)

Table 1 continued

Characteristic	Mean±SD or n (%)
Respiratory conditions	8790 (13.9)
Fibromyalgia	8768 (13.9)
Hypothyroidism	8493 (13.5)
Inflammatory polyarthritis	6385 (10.1)

SD standard deviation, *HMO* health maintenance organization, *PPO* preferred provider organization, *CDHP* consumer driven health plan, *QCI* Quan-Charlson index

[a] Comorbid conditions counted if a single occurrence of the code appeared, listed are conditions that affected at least 10% of the RA population. Comorbid autoimmune conditions included lupus erythematous (9.8%), dermatitis (6.2%), psoriatic arthritis (4.1%), psoriasis (3.2%), ankylosing spondylitis (1.4%), Crohn's disease (1.3%), and ulcerative colitis (1.1%)

osteoarthritis (31.1%) were among the most commonly observed comorbid conditions.

Treatment Patterns

Follow-up and Time to Treatments

Patients were followed for a mean of 3.5 ± 2.1 years after their index date, and 50% of patients were followed for at least 3 years (Table 2). The mean time from index date to first use of each DMARD treatment class was 94 ± 298 days for csDMARD ($n = 32,518$), 315 ± 448 days for biologic TNFi ($n = 10,360$), 757 ± 660 days for non-TNFi ($n = 2,228$), and $1,254 \pm 800$ days for JAKi users ($n = 274$). For patients who received a prescription pain medication, the mean time to treatment with pain medication was 194 ± 346 days.

DMARD Medication Use

Treatments were examined by DMARD class through 90 days from index date and through the entire post-index period (Fig. 2). Many patients (53.8%) received no DMARD therapy within 90 days after the index date; 44.9% of patients never received DMARD therapy during the entire follow-up period. However, examining rates by medical specialty, 78.9% of patients

Table 2 Follow-up time and time to treatment among patients newly diagnosed with rheumatoid arthritis ($n = 63{,}101$)

	Mean±SD/n (%)
Total follow-up time from index to end of follow-up (years)	3.5±2.1
≥2 years of follow-up	44,795 (71.0)
≥3 years of follow-up	31,293 (49.6)
≥4 years of follow-up	21,699 (34.4)
≥5 years of follow-up	14,657 (23.2)
Treatment characteristics	
Time to treatment (days from index date to first fill)	
csDMARD ($n = 32{,}518$)	94±298
Biologic TNFi ($n = 10{,}360$)	315±448
Biologic non-TNFi ($n = 2228$)	757±660
JAKi ($n = 274$)	1254±800
Time to pain medication (days) ($n = 49{,}123$)	194±346
Opioids ($n = 41{,}148$)	302±431
NSAIDs ($n = 32{,}935$)	303±458
COX 2 inhibitors ($n = 17{,}292$)	403±550
Acetaminophen ($n = 16$)	789±984
Muscle relaxants ($n = 315$)	449±495
Anticonvulsants ($n = 12{,}243$)	517±619
csDMARD use	
Number of patients with csDMARD use	32,518 (51.5)
Number of patients with csDMARD use diagnosed by rheumatologist	20,850 (64.1)
Total follow-up time (years)	3.7±2.1
From index to first use (days)	94±298
From first use to end of follow-up (days)	1244±765
Biologic use	
Number of patients with biologic use	11,250 (17.8)

Table 2 continued

	Mean±SD/n (%)
Number of patients with biologic use diagnosed by rheumatologist	7395 (65.7)
Total follow-up time (years)	3.9±2.2
From index to first use (days)	328±462
From first use to end of follow-up (days)	1092±760
From csDMARD (in those receiving csDMARD) (days)	388±446

treated by a rheumatologist received DMARD therapy at some point during follow-up, compared with just 36.3% of those seen by a non-rheumatologist. Within 90 days of index date, csDMARD therapy was the most prevalent (41.5%), followed by a biologic TNFi (4.5%), and a non-TNFi (< 1%) or JAKi (< 1%). When examining the entire follow-up period, there was a slight increase in csDMARD use (51.5%), with larger increases observed for biologic TNFi (16.4%) and biologic non-TNFi (3.5%) therapies. JAKi use remained rare, occurring in < 1% of the population.

Detailed Treatment Patterns

Detailed treatment patterns in the newly diagnosed RA population are depicted in Fig. 3. Among patients who received DMARD treatment ($n = 34{,}795$), 67.5% received only csDMARD during follow-up. Initiating a csDMARD and adding a TNFi as second-line therapy was the most common route to receiving biologic therapy (12.4% of treated patients), while treatment with a TNFi without ever receiving a csDMARD was the next most common (5.5%). While uncommon (1.2% of all DMARD-treated patients), non-TNFi use was most likely to occur after starting on a csDMARD, adding a TNFi, and then switching to a non-TNFi while remaining on a csDMARD.

Of patients who did not receive DMARD therapy ($n = 28{,}306$) during follow-up, many received symptomatic treatment; 56.5%
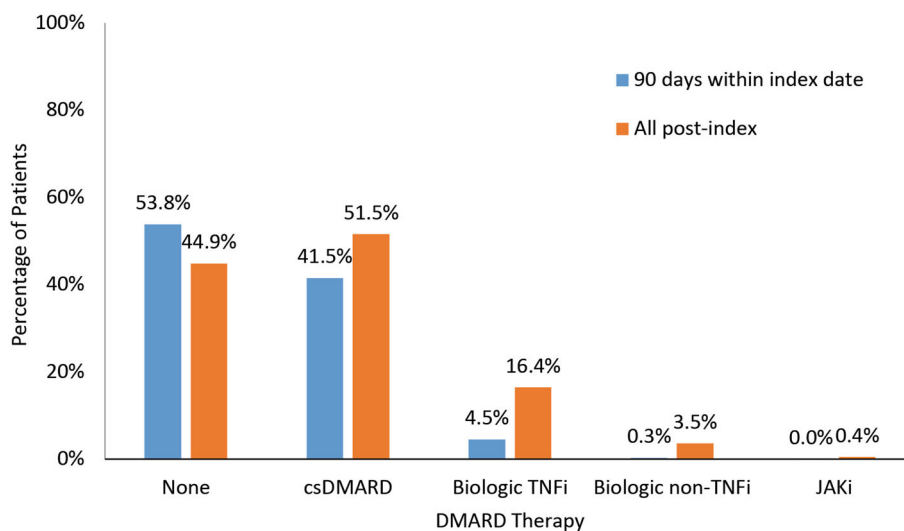
Fig. 2 DMARD medication use by class within 90 days of the index date (*blue bars*) and at any time during the post-index period (*orange bars*) (*n* = 63,101)

received opioids, 19.4% had evidence of chronic opioid use, and more than a third (37.9%) received steroids. In contrast, among those who received DMARD therapy (*n* = 34,795), 72.3% received opioids, 24.8% were chronic opioid users, and 72.9% received steroids at any time during follow-up.

Table 3 describes treatment line characteristics based on first DMARD treatment. The two most common first treatment changes were moving from a csDMARD to TNFi therapy either by adding on the TNFi therapy to the csDMARD regimen or switching from csDMARD therapy to TNFi monotherapy. Of 31,217 patients who started csDMARD as first-line therapy, 42.6% had no change, 32.8% discontinued, and 24.5% (*n* = 7656) either added on or switched to a new DMARD class. Among these 7,656 csDMARD-initiating patients who had second-line therapy, 62.2% had no additional therapy change, 14.5% discontinued, and 23.3% added or switched to the new therapy (i.e., moved to a third treatment line).

In patients who started a TNFi as first-line therapy (*n* = 3,303), 41.6% had no change in therapy class, 18.1% discontinued, and 40.3% either added or switched DMARD class. In 1,332 TNFi first-line users who had second-line therapy, 65.5% remained on their second-line therapy, 18.5% switched or added-on therapy,

and 15.9% discontinued. As for the group of patients who initiated a non-TNFi as first-line therapy (*n* = 339), 33.0% had no change, 27.7% discontinued, and 39.2% patients either added or switched to a new therapy. In non-TNFi first-line users moving to a second-line therapy (*n* = 133), 35.3% added on or switch therapy.

Occurrence of a second treatment change was relatively infrequent, as 62.2% of those on second-line therapy had no additional changes observed. The most common treatment change was discontinuation of therapy (15.0% of all second-line patients); thus just 22.8% of second-line patients moved on to a third line (*n* = 2,078, 6.0% of all treated patients). Three-quarters of third-line therapies contained a csDMARD, while TNFi (32.7%) and non-TNFi (47.4%) therapies were also observed. JAKi use rose above 1%, occurring in 5.7% of third-line treatment regimens.

DISCUSSION

This study provides insight into treatment patterns among newly diagnosed RA patients in a large managed-care setting and highlights important potential gaps in treatment. Treatment rates in our study population indicate that a large proportion of patients (nearly half of this
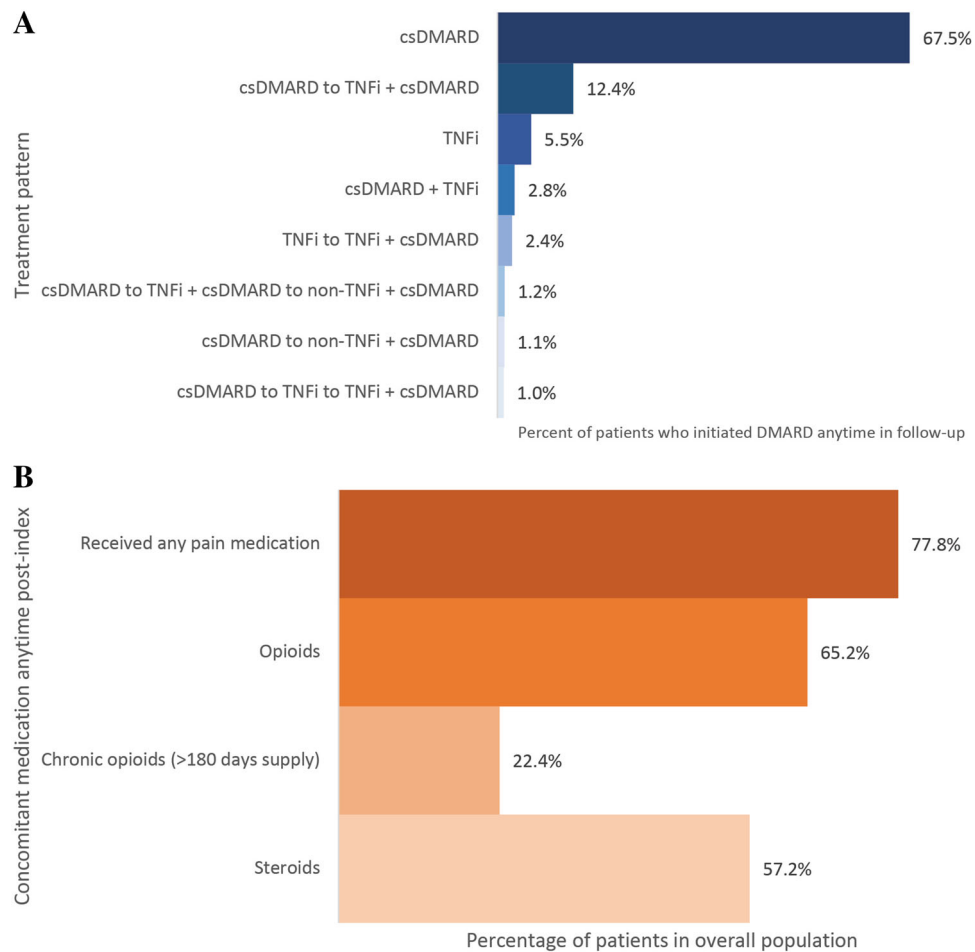
Fig. 3 Treatment patterns in patients with rheumatoid arthritis. **a** Treatment patterns within rheumatoid arthritis patients who received DMARD therapy ($n = 34,795$). Medications linked by a '+' symbol indicates the medication classes were received simultaneously. **b** Non-DMARD treatments in RA patients ($n = 63,101$)

cohort of patients with RA) did not receive guideline-recommended DMARD treatment. In the course of the study, only slightly more than one-half of the cohort received a csDMARD, less than one-fifth were treated with a biologic TNFi, and very few were treated with a biologic non-TNFi or a JAKi.

Among patients who received DMARD therapy, the use of csDMARD mono-class therapy was the most commonly initiated first-line treatment. Although the use of biologics was not prevalent during the first-line treatment, the proportion of biologics increased among patients who had second, third, and fourth lines of treatment. The use of JAKi increased during follow-up among patients who had more than

one treatment line, but the proportion remained quite low. However, this DMARD class was introduced into the market as a treatment option late in this study observation period.

Prior published studies have reported patterns of DMARD drug utilization for RA treatment similar to what was observed in our study—csDMARDs were the most commonly used treatment, and while fewer patients initiated treatment with biologics as expected [23, 24], their use increased over time; [24] furthermore, while our study showed a surprisingly low rate of DMARD use, other studies have reported comparable rates of DMARD treatment [1, 25–27].

Table 3 Treatment line characteristics based on first DMARD treatment in patients newly diagnosed with rheumatoid arthritis and treated with a DMARD therapy (n = 34,795)

	Overall (n = 34,795) Mean±SD/n(%)	First DMARD received[a]		
		csDMARD (n = 31,217) Mean ± SD/n(%)	TNFi (n = 3,303) Mean ± SD/n(%)	non-TNFi (n = 339) Mean ± SD/n(%)
First line characteristics	34,795 (100.0)	31,217 (100.0)	3303 (100.0)	339 (100.0)
Treatment line contains[b]				
csDMARD	31,217 (89.7)	31,217 (100.0)	56 (1.7)	12 (3.5)
TNFi	3303 (9.5)	56 (0.2)	3303 (100.0)	0 (0.0)
non-TNFi	339 (1.0)	12 (0.0)	0 (0.0)	339 (100.0)
JAKi	4 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Length of first-line therapy (days)	724 ± 693	730 ± 694	700 ± 694	466 ± 528
First treatment change characteristics				
No change	14,750 (42.4)	13,313 (42.6)	1373 (41.6)	112 (33.0)
Switch therapy	2587 (7.4)	2096 (6.7)	399 (12.1)	91 (26.8)
Add medication(s)	6529 (18.8)	5560 (17.8)	933 (28.2)	42 (12.4)
Discontinue treatment	10,929 (31.4)	10,248 (32.8)	598 (18.1)	94 (27.7)
Second line characteristics	9116 (100.0)	7656 (100.0)	1332 (100.0)	133 (100.0)
Treatment line contains[b]				
csDMARD	6888 (75.6)	5612 (73.3)	1197 (89.9)	84 (63.2)
TNFi	7888 (86.5)	6901 (90.1)	936 (70.3)	52 (39.1)
non-TNFi	885 (9.7)	704 (9.2)	143 (10.7)	44 (33.1)
JAKi	61 (0.7)	56 (0.7)	4 (0.3)	1 (0.8)
Length of second-line therapy (days)	748 ± 680	746 ± 672	795 ± 729	447 ± 582
Second treatment change characteristics				
No change	5673 (62.2)	4764 (62.2)	873 (65.5)	41 (30.8)
Switch therapy	877 (9.6)	700 (9.1)	141 (10.6)	36 (27.1)
Add medication(s)	1201 (13.2)	1084 (14.2)	106 (8.0)	11 (8.3)
Discontinue treatment	1365 (15.0)	1108 (14.5)	212 (15.9)	45 (33.8)
Third line characteristics	2078 (100.0)	1784 (100.0)	247 (100.0)	47 (100.0)
Treatment line contains[b]				
csDMARD	1552 (74.7)	1416 (79.4)	121 (49.0)	15 (31.9)
TNFi	679 (32.7)	524 (29.4)	138 (55.9)	17 (36.2)

Table 3 continued

	Overall (*n* = 34,795) Mean±SD/*n*(%)	First DMARD received[a]		
		csDMARD (*n* = 31,217) Mean ± SD/*n*(%)	TNFi (*n* = 3,303) Mean ± SD/*n*(%)	non-TNFi (*n* = 339) Mean ± SD/*n*(%)
non-TNFi	984 (47.4)	860 (48.2)	100 (40.5)	25 (53.2)
JAKi	119 (5.7)	109 (6.1)	7 (2.8)	3 (6.4)
Length of third-line therapy (days)	537 ± 546	528 ± 539	606 ± 598	535 ± 486
Third treatment change characteristics				
No change	1237 (59.5)	1072 (60.1)	137 (55.5)	28 (59.6)
Switch therapy	303 (14.6)	251 (14.1)	38 (15.4)	14 (29.8)
Add medication(s)	278 (13.4)	229 (12.8)	47 (19.0)	2 (4.3)
Discontinue treatment	260 (12.5)	232 (13.0)	25 (10.1)	3 (6.4)
Fourth line characteristics	581 (100.0)	480 (100.0)	85 (100.0)	16 (100.0)
Treatment line contains[b]				
csDMARD	359 (61.8)	285 (59.4)	65 (76.5)	9 (56.3)
TNFi	242 (41.7)	199 (41.5)	38 (44.7)	5 (31.3)
non-TNFi	218 (37.5)	184 (38.3)	30 (35.3)	4 (25.0)
JAKi	61 (10.5)	56 (11.7)	4 (4.7)	1 (6.3)
Length of fourth-line therapy (days)	447 ± 474	425 ± 454	567 ± 541	460 ± 602
Fourth treatment change characteristics				
No change	319 (54.9)	262 (54.6)	50 (58.8)	7 (43.8)
Switch therapy	116 (20.0)	96 (20.0)	14 (16.5)	6 (37.5)
Add medication(s)	278 (47.8)	229 (47.7)	47 (55.3)	2 (12.5)
Discontinue treatment	60 (10.3)	49 (10.2)	10 (11.8)	1 (6.3)

[a] Data stratified by first line JAKi use not shown due to insufficient sample size for analysis (*n* = 4)
[b] "Treatment line contains": among patients receiving a first-, second-, third-, or fourth-line of therapy, the following tabulates the numbers of each DMARD received during the line of therapy. Multiple treatments may be present during any given treatment line

Our results showed that RA patients diagnosed by rheumatologists had higher rates of DMARDs prescribed (79%) compared with only slightly more than a third of the patients diagnosed by non-rheumatologists. The higher rate of DMARD use among those treated by a rheumatologist is consistent with data from the ACR's RISE (Rheumatology Informatics System for Effectiveness) registry of rheumatology practices, which showed that 91% of RA patients were on a DMARD at their last clinical encounter [28]. This could help to explain some

of the inconsistencies observed in the DMARD treatment patterns in this study relative to treatment recommendations, as less than half of the RA patients were diagnosed by a rheumatologist.

This difference in DMARD treatment rates by medical specialty may be driven by three factors: first, rheumatologists are likely more familiar and up to date with RA treatment recommendations and thus more likely to prescribe appropriate therapy; second, claims-based diagnoses coming from a rheumatologist for RA may be more accurate than those coming from non-rheumatologists in which rule-out diagnoses may be more common; and third, non-rheumatologists may exhibit less comfort with prescribing or managing RA patients on DMARD therapies. Further commentary on the limitations of using administrative claims to identify RA patients can be found in the 'Strengths and Limitations' section below.

The use of steroids and pain medications, including chronic opioid use, in the DMARD untreated population, while not as high as in the DMARD-treated patients, is problematic. Symptomatic treatment alone, without use of DMARDs, is not effective in preventing further joint damage in RA. Khanna et al. reported similar results in a Medicare population: nearly 68 and 48% of these RA patients had ≥ 1 prescription fill for opioid analgesics and steroids, respectively [23]. In the overall study population, more than two-thirds received opioids, with slightly more than one-fifth considered chronic users, and more than a half of all patients received steroids. The use of opioids and steroids was more common in those patients receiving DMARD therapy at any time during follow-up compared with those who never received a DMARD during the study period. Unfortunately, it is a limitation of claims data that reasons for use of medications cannot be explicitly determined. For instance, the presence of opioid use does not necessarily mean they were being used for treatment of RA symptoms, but may have been used for other causes of pain unrelated to their RA, such as low back pain or surgery. The claims data do not specify a diagnosis for which a medication was prescribed, only that it was dispensed.

While symptomatic management alone is inconsistent with treatment recommendations and quality metrics for RA management, it could well be part of a broader trend in which 3–4% of adult Americans are treated with opioids for pain control [29]. While clinical studies [27] and surveys [30–32] have reported short-term pain relief associated with opioid use, few studies have investigated longer-term outcomes for opioid analgesics for pain therapy [30]. While pain management is a key aspect to successfully treating RA, current data inform of considerable death and addiction-related risks— more than 165,000 people died from opioid overdosing related to pain management in the US during 1999–2014, [31] an estimated 1.9 million people abused or were dependent on opioid pain medicines during 20 [13, 33] and in 2014, more than 10 million people in the US reported using prescription opioids for non-medical reasons [34].

Also concerning is the relatively frequent use of steroids in this patient cohort. Even at low doses, steroids such as prednisone are associated with elevations in blood pressure, blood glucose, and lipid levels, as well as increased osteoporosis risk [35]. An assessment of steroid use in a cohort mirroring the US population's proportion of women suggests that care must be exercised to ensure that treatments do not exacerbate conditions like osteoporosis and attendant bone fracture risks [1, 5].

These results may help to inform decision-making by stakeholders engaged in the management of RA. Future treatment patterns may respond to an increased awareness of the treatment recommendations and the introduction of new therapies and therapeutic indications on formulary decisions and payment structures.

DMARDs are recommended for all newly diagnosed patients according to ACR treatment recommendations [9, 36, 37]. In addition, DMARD use among patients diagnosed with RA is one of the quality metrics established by the National Quality Forum [38], the Center for Medicare and Medicaid (CMS) Physician Quality Reporting System [39], and the National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set [40], which require reporting of the percentage of

adults with RA treated with DMARD therapy—a metric which also factors into CMS Star ratings [41]. The results observed in this study raise an important concern of a potential care quality gap in RA management.

Strengths and Limitations

The use of a large, geographically diverse, administrative claims database provided this study with several key strengths. First, the data allowed us to retrospectively observe the longitudinal treatment patterns in newly diagnosed RA patients over a period of 1–9 years (mean, 3.5 years) after their initial RA diagnosis. Second, a sensitivity analysis limiting the observation period to 2010 onward showed consistent results, and thus the findings are a reflection of historical treatment patterns over the past decade as well as recent treatment practices. Finally, these data provide real-world evidence of disease management rather than being limited to the strict guidelines of a clinical trial or other controlled experiment. This study includes a contemporary patient population and presents a view of the current treatment landscape.

While there were clear strengths of this study, these findings must be viewed against some important limitations. First, we identified patients newly initiating RA medication after a 6-month period in which there were no claims for RA medications or RA diagnoses before the index RA medication claim/RA diagnosis code. This approach may not have captured the true incident RA population, i.e., prevalent RA cases may be included, and as a result, our results may be conservatively biased. Second, the minimum continuous enrollment required was 12 months; however, patients were followed beyond the 12-month timeframe until the end of the study period, and their patterns later into enrollment may be affected by loss to follow-up. The mean observation period of 3.5 years from index may offer insufficient time to fully observe the actual use of more advanced DMARD therapies as biologics or JAKi. Finally, our analysis focused on commercially insured patients, possibly under-representing elderly patients enrolled in Medicare.

Furthermore, diagnosis codes are good indicators but not guarantees of the presence of disease as they may be subject to miscoding or may be included as a rule-out criterion. As noted, the reliance on administrative claims (a combination of ICD-9 codes from medical claims and claims for DMARD therapy), without access to medical records, is potentially limiting in identifying RA patients. Studies examining the validity of administrative claims to identify RA patients have found mixed results depending on the algorithm used. Typically the use of multiple claims with RA diagnoses improved the positive predictive value of the definitions, and requiring a diagnosis from a rheumatologist improves the algorithm even further [42–44]. Studies that utilized a more focused code list of RA diagnoses, such as the one used in this study, tended to have higher validity compared with those that used all ICD-9 codes starting with 714 [44]. While our definition of RA may include some patients who do not truly have RA, the algorithm was developed with the goal of minimizing this occurrence. We also conducted a sensitivity analysis using a much more restrictive (i.e., specific) definition of RA, and study results were not fundamentally different.

In general, claims databases are subject to common limitations including the inability to account for medications from other sources such as over-the-counter purchases or samples from providers. Claims data provide limited insight into the clinical status of patients, particularly their severity or activity of their disease and the process surrounding moving onto DMARD therapy—for example, whether DMARD was offered then declined; prescribed and never filled; filled and not used; or not offered at all. Similarly, it is unknown whether patients not seen by a rheumatologist were referred but declined, or not referred. Reasons for initiation of one DMARD class over another, such as the selection of a non-TNFi or a JAKi as the index DMARD therapy, are unknown, and these patients may differ from the general RA population.

CONCLUSIONS

Nearly half (45%) of the RA patients in our study did not receive DMARD therapy at any time during the follow-up period, while the use of pain medications and steroids was high. The most common DMARD treatment pattern was receiving only csDMARD monotherapy with a much smaller portion receiving biologic therapy at any time. Less than half of patients were diagnosed with RA by a rheumatologist and is the most likely reason for the variance in adherence to treatment recommendations. Future research efforts may build upon this work to understand why this treatment gap exists, to develop solutions to address this unmet need, and to ultimately understand how treatment patterns in RA patients are associated with disease activity, quality of life, and clinical and economic outcomes.

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