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Real-world treatment patterns for repository corticotropin injection in patients with rheumatoid arthritis

Howard Busch[1], George J Wan[2], John Niewoehner[2], Parul Houston[3], Yujie Su[4], Cassie Clinton[4], Mary P Panaccio[2]

[1]American Arthritis and Rheumatology Associates LLC, Loxahatchee, FL, USA; [2]Mallinckrodt Pharmaceuticals, Hampton, NJ, USA; [3]SSI Strategy, Parsippany, NJ, USA; [4]University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

Introduction: Repository corticotropin injection (RCI, Acthar® Gel) is a naturally sourced mixture of adrenocorticotropic hormone analogues and other pituitary peptides with anti-inflammatory and immunomodulatory effects. In a recent clinical trial, RCI was safe and effective for the treatment of refractory rheumatoid arthritis (RA). This study aims to describe real-world use and outcomes of patients with RA who were prescribed RCI in clinical practice through retrospective analysis of an electronic medical record database.

Methods: Patients with RA who were prescribed RCI were identified through the Columbus™ electronic medical record repository, representing approximately 100 rheumatology practices. Demographics, medications, comorbidities, disease histories, laboratory evaluations, clinical outcomes and patient-reported outcomes were evaluated from 12 months pre-RCI to 12 months post-RCI initiation.

Results: The RCI cohort (*n*=63) comprised predominantly white women, aged 54 years on average, at 6 years from RA diagnosis, with high disease activity at baseline according to Clinical Disease Activity Index (CDAI) and Routine Assessment of Patient Index Data 3 (RAPID3) scores. Within the 12 months pre-RCI initiation, 87% of patients were prescribed disease-modifying antirheumatic drugs and 67% were prescribed glucocorticoids. Twelve months post-RCI initiation, glucocorticoid, opioid and non-steroidal anti-inflammatory drug prescriptions decreased; disease-modifying antirheumatic drug prescriptions remained stable. Reductions in CDAI, RAPID3, physician global assessment, tender joint count, swollen joint count, and pain visual analogue scale scores were observed 12 months post-RCI initiation. Few discontinuations were due to side effects. Study limitations included small sample size and incomplete electronic medical record data.

Conclusion: These findings support the safety and effectiveness of RCI for short-term adjunctive treatment of refractory RA and provide patient-management insights from routine clinical practice.

Keywords: Acthar Gel, disease-modifying antirheumatic drugs, DMARDs, glucocorticoids, real-world evidence, repository corticotropin injection, rheumatoid arthritis.

Citation

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that causes synovial inflammation and progressive joint damage.[1] There is a large unmet need for patients with refractory RA who display persistently high RA disease activity or flares despite treatment with standard-of-care therapies.[1] Real-world evidence is necessary to support the effectiveness of RA drugs in a clinical setting and to identify appropriate patient populations who are likely to experience a clinical response to such treatments.[2,3]

Repository corticotropin injection (RCI, Acthar® Gel) is approved by the US Food and Drug Administration as a short-term adjunctive therapy for RA flares or exacerbations.[2] Patients with RA who are non-responsive or cannot tolerate the side effects of glucocorticoids (GCs) or disease-modifying antirheumatic drugs (DMARDs) are appropriate candidates for RCI therapy.[4] RCI is a naturally sourced mixture of adrenocorticotropic hormone (ACTH) analogues and other pituitary peptides.[2] The RCI manufacturing process converts a porcine pituitary extract with low ACTH levels into a mixture of modified ACTH and related peptide analogues solubilized in gelatin.[2]

RCI engages all five melanocortin receptors (MCRs) and has demonstrated immunomodulatory and anti-inflammatory effects.[5–8] RCI stimulates endogenous cortisol production by activating MC2R on adrenocortical cells and has steroid-independent mechanisms by activating MC1R, MC3R, MC4R and MC5R on immune cells and other tissues throughout the body.[6,9,10] Preclinical studies have shown that RCI is a partial agonist of MC5R and a full agonist of all other MCRs.[8] Of the MCRs for which it acts as a full agonist, RCI has its lowest activity at MC2R, suggesting that it predominantly functions through the direct modulation of immune cells and other tissues, rather than through endogenous cortisol production from the adrenal cortex.[8] Other published studies have reported that RCI may have different adverse effects than GCs,[4] which has prompted a recent label change for RCI, removing previous language stating that common adverse reactions for RCI are similar to those of GCs.[2,4,11]

Several clinical and economic benefits of RCI have been demonstrated in the treatment of RA and other inflammatory conditions.[4,12–19] Patients with RA receiving RCI therapy experienced a reduction in swollen joint count (SJC) and tender joint count (TJC) as well as improved physical function and health-related quality of life.[13,15,20] Patients with RA or systemic lupus erythematosus who received RCI had lower rates of hospitalization, emergency department visits and outpatient services.[17,19]

This study builds upon several previous RA studies that showed RCI to be safe and effective.[4,13–15,20,21] A randomized, double-blind, placebo-controlled trial of patients with RA and active disease despite receiving GC and DMARD therapy demonstrated that RCI decreased disease activity in most patients, improved patient-reported disability, fatigue and work productivity outcomes, and was safe.[4] Sixty-three percent of patients experienced low disease activity with RCI, which was maintained for 3 months after RCI discontinuation.[4] A retrospective medical record analysis of RCI reported improvement in 78.1% of patients with RA based on physician's impression of change.[20] Another analysis of a rheumatology electronic medical record (EMR) database reported significant improvements in RA disease activity, functional status and pain with a decreased need for concomitant medications for up to 1 year following initiation of RCI therapy.[21] The benefit–risk profile of RCI is consistent across well-controlled clinical trials,[4] open-label studies[1,13–15] and a retrospective analysis.[20] The current study provides additional supportive real-world rheumatology practice data on disease-assessment and prescribing patterns, dosing, clinical effectiveness and tolerability, which are important for understanding performance in patients with complex disease in clinical practice.[3,22,23]

Guidelines on clinical quality measures published by the American College of Rheumatology (ACR) and the US Centers for Medicare and Medicaid Services (CMS) recommend performing functional status assessments (e.g. Routine Assessment of Patient Index Data 3 (RAPID3)) and/or clinical disease activity measures (e.g. Clinical Disease Activity Index (CDAI)) routinely, at least annually, or more frequently if the patient displays active disease. Therefore, the percentage of patients who underwent these assessments in the 12 months post-RCI initiation can be used to determine how closely healthcare providers followed these guidelines.

This study was designed as a descriptive analysis to better understand real-world utilization and outcomes of RCI in patients with refractory RA that did not adequately respond to standard-of-care therapies using EMR data from a large US rheumatology practice network, where more in-depth patient-reported outcomes (PROs) and clinical disease activity assessments were available. The study objectives were to describe demographic and clinical characteristics of patients with RA to whom RCI was prescribed in real-world clinical practice; to identify patterns of dose changes and discontinuations related to RCI treatment; and to record any changes in clinical scores, PROs and concomitant medication prescribed before and after RCI initiation.

Methods

Ethics and compliance

The management of study data conformed to all applicable Health Insurance Portability and Accountability Act rules. All data were de-identified throughout the study to preserve patient anonymity and confidentiality. This observational study was conducted with Institutional Review Board approval from Advarra. Because this was a retrospective study, the Institutional Review Board determined that patient informed consent was not required.

Study design

This was a descriptive, non-interventional, US-based, retrospective EMR database analysis in patients initiating RCI therapy for the treatment of refractory RA. There was no direct contact with patients. The entire study period was from October 1, 2015, to May 31, 2020, with study inclusion beginning October 1, 2016, and ending May 31, 2019, to allow for demographic and clinical data to be assessed for 12 months before and after RCI initiation (i.e. after the first RCI prescription date with no evidence of prior prescriptions). Data were acquired from the Columbus™ repository of EMRs obtained through BendCare, LLC, in August 2020 from approximately 100 rheumatology practices associated with the American Arthritis and Rheumatology Associates. The database extracted EMR data that included diagnoses, current and past medications, lab results, biometric data and all rheumatology visit information. The 12 months post-RCI initiation began the day after the first RCI prescription and continued for 12 months, including RCI treatment cessation, loss to follow-up or the end of the study period.

The variables analysed during the 12 months pre-RCI initiation were patient demographics, comorbidities, disease history and prescribed medications. Additional data collected in the 12 months before and after RCI initiation included prescribed treatments as well as RCI dose, frequency and duration. RCI treatment-related clinical disease activity measures, PROs and clinical quality measures (i.e. percentage of patients receiving a functional or clinical status assessment annually) were evaluated within 7 days before or after RCI initiation and 12 months post-RCI initiation. If feasible, these data were collected following the discontinuation of RCI treatment. Further details on the analysis of outcomes in the post-RCI initiation period are described below.

Eligibility criteria

Patients were included if they were ≥18 years of age at the RCI initiation visit and had ≥2 outpatient RA diagnoses (including International Classification of Diseases M05*, RA with rheumatoid factor (RF); or M06*, RA without RF; ignoring M061, adult-onset Still's disease; and ignoring M064, inflammatory polyarthropathy) with one or more prescriptions or administration of any DMARD during the entire study period. Patients were required to fulfil the RA cohort inclusion criteria on or prior to RCI initiation and to have clinical EMR data available for the 12 months before and after RCI initiation (Figure 1).

Demographics, clinical characteristics, outcomes and quality measures

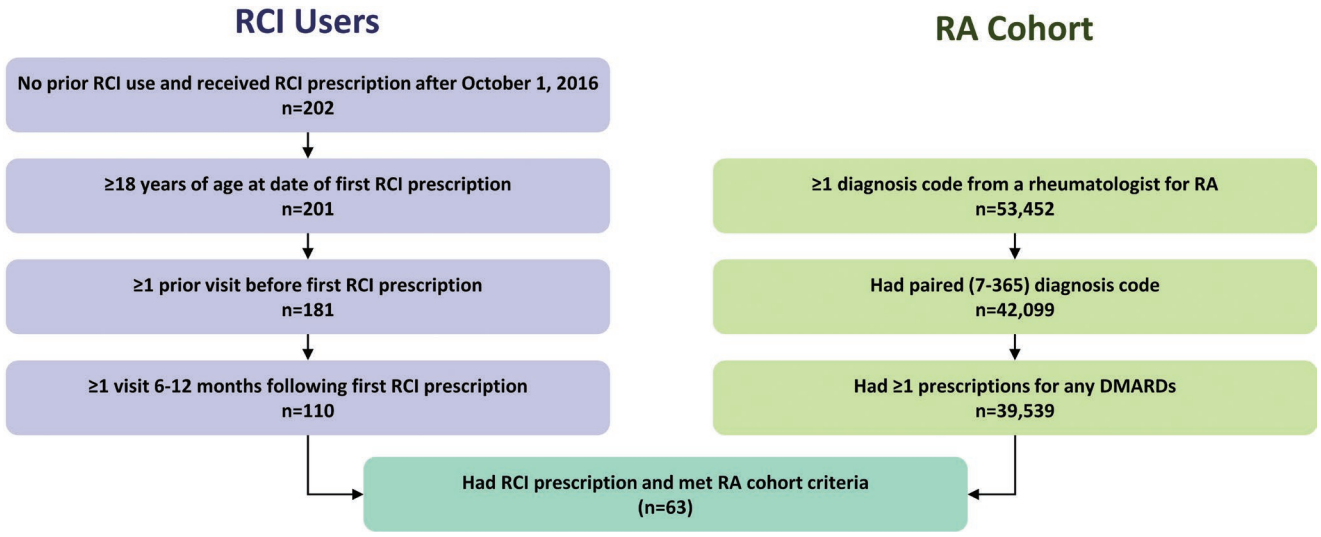
Patient demographics and clinical characteristics were assessed using all available data on or before the RCI initiation.

Demographics consisted of age, sex, race, US geographic region and insurance type. Clinical characteristics included time since diagnosis, RA duration, weight, body mass index (BMI) and comorbidities.

Mean changes in clinical outcomes and PROs were determined by comparison of RA disease activity, PROs and symptoms assessed within 7 days before or after RCI initiation to those obtained from the 12 months post-RCI initiation. This 7-day period for clinical disease activity and PRO assessments ensured that the measure closest to RCI initiation was used to evaluate RCI effectiveness. The presence of RA was determined by the observation of clinical signs such as a high number of tender and swollen joints. Disease-related features included RA seropositivity determined by detection of serum RF and/or anticyclic citrullinated protein (anti-CCP) antibodies; RA disease duration and CDAI scores; TJC and SJC using a 28-joint count; levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); and the multibiomarker disease activity score.

Physician and patient global assessments were reported using a 10-point Likert scale. PROs were evaluated by RAPID3 (remission, ≤3.0; low activity, >3.0 to ≤6.0; moderate activity, >6.0 to ≤12.0; high activity, >12 to 30) and the pain visual analogue scale (VAS; mild pain, <3.5; moderate pain, ≥3.5 to <7.5; severe pain, 7.5 to 10).[24–29] RA disease activity was determined by CDAI scores (remission, ≤2.8; low activity, >2.8 to ≤10.0; moderate activity, >10.0 to ≤22.0; high activity, >22.0 to 76.0),[25,30,31] CRP levels and ESR. RCI effectiveness was determined by calculation of the changes in mean values of assessed measurements from 7 days before or after RCI initiation to the 12 months post-RCI initiation. Paired measures comparisons of clinical values pre-RCI and post-RCI initiation only included patients who had both measures in their EMR. This study employed two clinical

Figure 1. Study flow diagram.



DMARDs, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; RCI, repository corticotropin injection.

measures (physician global assessment and CDAI) and one patient-reported measure (RAPID3) to assess disease severity. Quality measures were assessed by determining the percentage of patients who had a RAPID3 or CDAI recorded in their EMRs in the 12 months post-RCI initiation.

RA treatment patterns

Treatment information obtained from EMR data was used to evaluate patient prescription patterns of standard RA medications 12 months before and after RCI initiation. This included the number of unique DMARD prescriptions per patient, GC prescriptions and dosage (low, ≤7.5 mg/d; moderate, >7.5 to 15 mg/d; or high, >15 mg/d), and prescriptions of non-steroidal anti-inflammatory drugs (NSAIDs) or opioids. DMARDs were classified as conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs) or targeted synthetic (tsDMARDs). Supplementary Table 1 (available at: https://www.drugsincontext.com/wp-content/uploads/2022/02/dic.2021-10-4-Suppl.pdf) describes the classification of RA medications used in the analysis.

RCI treatment patterns

Captured in the EMRs were a number of RCI prescription renewals; number and magnitude of dose adjustments per patient; time from RCI initiation to dose change; duration of RCI treatment from initiation to discontinuation; loss to follow-up, end of prescribed supply of RCI or end of study period; reason for RCI discontinuation; and number of patients switching from RCI to other therapies. Physicians determined the reasons for discontinuation based on their interactions with patients during office visits.

Statistical analysis

All data processing and statistical analyses were performed using SAS software package version 9.4 (SAS Institute Inc.) and R 4.0.3. Descriptive statistics (number of patients, mean, median and standard deviation for continuous variables or frequency counts and percentages for categorical variables) were used to describe patient demographics, clinical characteristics, treatment patterns, and clinical outcomes. Additional frequency statistics were reported for the 'unknown/missing/not recorded' responses to each of the data capture elements. Once all necessary clinical data were received, they were validated for accuracy and completeness prior to analysis and reporting.

Using EMR data only from patients with documented assessment values within both 7 days before or after RCI initiation and discontinuation within 12 months post-RCI initiation, RCI effectiveness was evaluated using repeated paired measures analysis to calculate mean changes in the presence of disease-related features, including clinical, functional and PRO assessments. All analyses are descriptive, and no formal statistical probability tests were conducted due to the small sample size.

Results

Patient profiles pre-RCI initiation

Demographics, clinical characteristics and treatments

Of the 63 patients prescribed RCI in the Columbus™ database who met the study inclusion criteria, the majority were white (81%), women (88.9%), older than 50 (54.0±10.7) years, living in the southern US (77.8%), and had either commercial insurance (41.3%) or Medicare (27%) (Table 1). Mean time since diagnosis was 6.0±2.8 years. The most prevalent comorbidities were osteoarthritis (30.2%), Sjögren's syndrome (20.6%) and osteoporosis (14.3%). Almost half of the patients were categorized with obesity (48.3%), with a mean BMI of 30.4±7.8 kg/m^2. RF and anti-CCP data were commonly missing (65.1%) during the study period. The ICD-10 diagnosis code M05* was used as a surrogate to allow imputation for RA seropositivity and 51% of patients were seropositive.

All patients had recorded DMARD prescriptions at some point within 4 years pre-RCI initiation, and the majority of patients maintained active DMARD prescriptions during the 12 months pre-RCI initiation (87.3%; Table 1). Approximately 57%, 13% and 57% of patients were prescribed csDMARDs, tsDMARDs and bDMARDs, respectively. During the 12 months pre-RCI initiation, patients were prescribed an average of 1.8 unique DMARDs, and GCs were prescribed to 66.7% of patients. One-third of all patients, or half of the patients prescribed steroids, received prescriptions for a moderate (≥7.5 to 15 mg/d) to high (>15 mg/d) regimen of GCs, and the mean prescribed GC dose was 8.4±5.6 mg/d. The proportion of patients prescribed NSAIDs or opioids was 27% and 41.3%, respectively (Table 1).

RCI treatment patterns

RCI starting dose, treatment duration and dose changes

Most patients (74.6%) were using the recommended RCI dose of 80 units twice per week for 10.3±6.8 months. The proportion of patients prescribed less or more than the recommended dose was the same (12.7%) (Table 2). Only a small number of patients had ≥1 dose change (6.3%); two patients decreased and two increased their prescribed RCI dosages.

Reasons for RCI discontinuation

Physicians reported that patients usually discontinued RCI treatment because it was no longer required (47.8%). A small proportion of patients (4.3%) reported side effects as a reason for discontinuation. Lack of efficacy related to RCI treatment was not reported as a reason for discontinuation (Table 2).

Table 1. Demographics, clinical characteristics and treatments of patients who met the RA cohort inclusion criteria (*n*=63) during the 12 months pre-RCI initiation.

Demographics	***n* (%) or mean ± SD**
Age (years)	54.0±10.7
18–34	1 (1.6)
35–44	12 (19.0)
45–54	15 (23.8)
55–64	23 (36.5)
65+	12 (19.0)
Women	56 (88.9)
Race	
White	51 (81.0)
Black/African American	5 (7.9)
Asian	0 (0.0)
Unknown	7 (11.1)
Geographic region	
South	49 (77.8)
Northeast	3 (4.8)
Midwest	0 (0.0)
West	11 (17.5)
Health insurance type	
Commercial	26 (41.3)
Medicare	17 (27.0)
Medicare Advantage	7 (11.1)
Medicaid	7 (11.1)
Other	6 (9.5)
Clinical characteristics	***n* (%) or mean ± SD**
Time since diagnosis (y) (*n*=32)	6.0±2.8
Comorbidities[a]	
Anaemia	7 (11.1)
Anxiety	3 (4.8)
Chronic pulmonary disease	4 (6.3)
Carpal tunnel syndrome	2 (3.2)
Diabetes mellitus	3 (4.8)
Hypertension	1 (1.6)
Interstitial lung disease	4 (6.3)
Osteoarthritis	19 (30.2)
Osteoporosis	9 (14.3)
Sjögren's syndrome	13 (20.6)
Weight (kg)[a] (*n*=29)	83.1±21.1
BMI[a] (*n*=29)	30.4±7.8
Eutrophic (<25 kg/m^2)	6 (20.7)
Overweight (25–30 kg/m^2)	9 (31.0)
Obese (>30 kg/m^2)	14 (48.3)
Seropositive for RA (imputed)[b,c]	32 (50.8)
Prescribed treatments pre-RCI initiation[a]	***n* (%) or mean ± SD**
DMARDs	55 (87.3)
bDMARDs	36 (57.1)
csDMARDs	36 (57.1)
tsDMARDs	8 (12.7)
None of these	8 (12.7)
Unique DMARDs per patient[b] (*n*=55)	1.8±1.2
GCs	42 (66.7)
High (>15 mg/d)	6 (9.5)
Moderate (>7.5–15 mg/d)	15 (23.8)
Low (≤7.5 mg/d)	21 (33.3)
No prescription recorded	21 (33.3)
GC dose (mg/d)	8.4±5.6
NSAIDs	17 (27.0)
Opioids	26 (41.3)

[a]Measured within the 12 months pre-RCI initiation.
[b]Subgroup analysis, based on data availability.
[c]Seropositivity imputed using ICD-10 diagnosis code M05* as described in the Methods section.

bDMARDs, biologic DMARDs; BMI, body mass index; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; GCs, glucocorticoids; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; tsDMARDs, targeted synthetic DMARDs; VAS, visual analogue scale.

Clinical outcomes assessment

Disease activity, PROs and clinical quality measures

A subset of patients had disease activity and PRO data recorded for the 7 days before or after RCI initiation and during the 12 months post-RCI initiation, which were compared to evaluate the effectiveness of RCI treatment (Table 3). About 27% of patients had measures recorded for CDAI, TJC and SJC within 7 days before or after RCI initiation and during the 12 months post-RCI initiation (Table 3). Data were also limited for RAPID3 (22%), pain VAS scores (17%) and physician global assessment (11%). Elevated scores for CDAI and RAPID3 indicated that most patients had high RA disease activity within 7 days before or after RCI initiation, despite patients being prescribed standard-of-care therapies. The mean SJC was lower than the observed TJC within 7 days before or after RCI initiation, whilst the average pain VAS score was 7 out of 10.

Table 2. RCI treatment patterns, treatment duration and reasons for discontinuation in the 12 months post-RCI initiation.

RCI treatment patterns	*n* (%)
RCI starting dose	
80–120 unit/week (less than the recommended dose)	8 (12.7)
80 units twice/week (recommended dose per package insert)	47 (74.6)
240–400 unit/week (greater than the recommended dose)	8 (12.7)
Reasons for discontinuation (*n*=46)	
No longer required	22 (47.8)
Lack of efficacy	0 (0.0)
Side effects	2 (4.3)
Others[a]	9 (19.5)
Unknown	13 (28.4)
RCI treatment duration (*n*=63)	**Mean ± SD**
Cumulative duration of drug dispensed (months)[b]	14.0±12.9
Cumulative duration of prescription (months)[c] (*n*=63)	10.3±6.8

[a]Includes erroneous and payer mandate.
[b]Sum of all durations of exposure of each of the prescriptions, ignoring overlapping dates (this assumes that all refills provided to the patient were filled and taken).
[c]Last prescription's effective date minus first prescription's effective date plus duration of exposure from the last prescription, assuming that all refills provided to the patient were filled and taken.

RCI, repository corticotropin injection.

Table 3. Changes in disease activity assessments and PROs from 7 days before or after RCI initiation to 12 months post-RCI initiation.

Disease activity or PRO assessment	Observed values ±7 days from RCI initiation, mean ± SD (*n*)	Change from ±7 days from RCI initiation to 12 months post-RCI initiation,[a] mean ± SD (*n*)
CDAI[b]	23.5±10.0 (19)	−6.6±11.3 (17)
RAPID3[c]	17.6±6.0 (15)	−1.2±4.4 (14)
SJC	6.1±5.2 (19)	−1.3±5.5 (17)
TJC	13.3±6.4 (19)	−4.1±7.1 (17)
Pain VAS score[d]	7.0±2.9 (11)	−0.5±1.4 (11)
Physician global assessment	5.6±2.5 (8)	−0.7±1.8 (7)

[a]Only patients with assessment values documented within the 7 days before or after RCI initiation and 12 months post-RCI initiation were included in these descriptive paired measures statistics.
[b]CDAI minimum clinically important difference (MCID): 6.5-point decrease represents moderate improvement.[30]
[c]RAPID3 MCID: 3.8-point decrease represents moderate improvement.[36]
[d]Pain VAS score MCID: 0.5–1.1-point decrease represents moderate improvement.[29]

CDAI, Clinical Disease Activity Index; PRO, patient-reported outcome; RAPID3, Routine Assessment of Patient Index Data 3; RCI, repository corticotropin injection; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

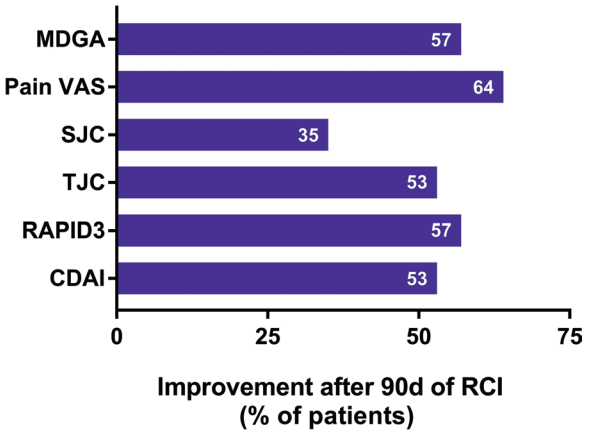
At 12 months post-RCI initiation, a reduction in mean CDAI score (−6.6±11.3) was observed, which exceeded the threshold for a minimum clinically important difference (MCID) previously reported as a decrease of 6.5 (Table 3).[30] Less prominent decreases in mean RAPID3, pain VAS score and physician global assessment were also observed; however, the pain VAS score reduction also met the lower range of the MCID threshold of −0.5.[29] Both TJC and SJC decreased, with a greater magnitude of reduction for TJC than for SJC (Table 3). Of the patients with RA who had disease activity or PROs assessed at a 90-day follow-up visit, most saw improvements in clinical outcomes after 90 days of RCI treatment compared to values collected 7 days before or after RCI initiation (Figure 2). Clinical outcomes and PROs observed in ≤6 patients (i.e. patient global assessment, ESR, CRP, multibiomarker disease activity) were not reported.

Analysis of clinical quality measures showed that 25 (40%) patients had CDAI, TJC or SJC assessed; 49 (78%) patients had RAPID3 assessed; 45 (71%) had their pain VAS evaluated; and 11 (17%) received a physician global assessment within 12 months post-RCI initiation despite most of these patients reporting moderate to severe RA.

GC usage and dose

Relative to the 12 months pre-RCI initiation, the proportion of patients prescribed high-dose and moderate-dose GCs decreased from 14% to 2% and from 36% to 17%, respectively, in the 12 months post-RCI (Figure 3). Moreover, 71% of patients were prescribed low-dose GCs, whereas 10% of patients had no further GC prescriptions recorded within 12 months post-RCI initiation (Figure 3). The number of patients with a prescription of any dose of GCs decreased from 42 (67%) to 38 (60%) (Figure 4) with a mean prescribed GC dose of 8.3±5.3 mg/d. Of those patients prescribed GCs during the 12 months pre-RCI initiation (*n*=42), 40%

Figure 2. Proportion of patients showing any improvement in clinical assessments or patient-reported outcomes after 90 days of treatment with RCI compared to values observed within 7 days before or after RCI initiation.



Data from a subset of patients with RA for whom assessments were evaluated both within ±7 days of RCI initiation and at a 90-day post-RCI initiation follow-up visit. MDGA, *n*=7; pain VAS, *n*=11; SJC, *n*=17; TJC, *n*=17; RAPID3, *n*=14; CDAI, *n*=17.
CDAI, Clinical Disease Activity Index; MDGA, physician global assessment; RAPID3, Routine Assessment of Patient Index Data 3; RCI, repository corticotropin injection; SJC, swollen joint count; TJC, total joint count; VAS, visual analogue scale.

were prescribed lower dosing regimens of GCs 12 months post-RCI initiation.

DMARDs

DMARD prescriptions remained relatively stable throughout the study. A similar number of patients were prescribed DMARD treatment 12 months pre-RCI initiation (*n*=55, 87%) as during the 12 months post-RCI initiation (*n*=54, 86%). These patients' records indicated that they were prescribed approximately the same number of unique DMARDs during the 12 months pre-RCI initiation (1.8±1.2 DMARDs) and 12 months post-RCI (1.6±1.2 DMARDs). Five patients had stopped receiving prescriptions for csDMARDs, four patients began receiving prescriptions for bDMARDs or tsDMARDs, and one patient had no recorded DMARD prescriptions in the 12 months post-RCI initiation.

NSAID and opioid use

Medications regularly prescribed for the management of RA flare-associated pain include NSAIDs and opioids.[32,33] The proportion of patients prescribed opioids or NSAIDs was higher during the 12 months pre-RCI initiation (41% and 27%, respectively) than during the 12 months post-RCI initiation (29% and 19%, respectively; Figure 4).

BMI

The mean change in BMI at 12 months post-RCI initiation was 0.6±2.5 kg/m^2 (*n*=28). BMI was unchanged in 89.2% of patients from whom BMI data were gathered. Only 2 (7.1%) patients recorded increased BMI. Weight gain typically occurs following prolonged GC use; however, no significant weight gain was associated with RCI prescriptions in these patients.

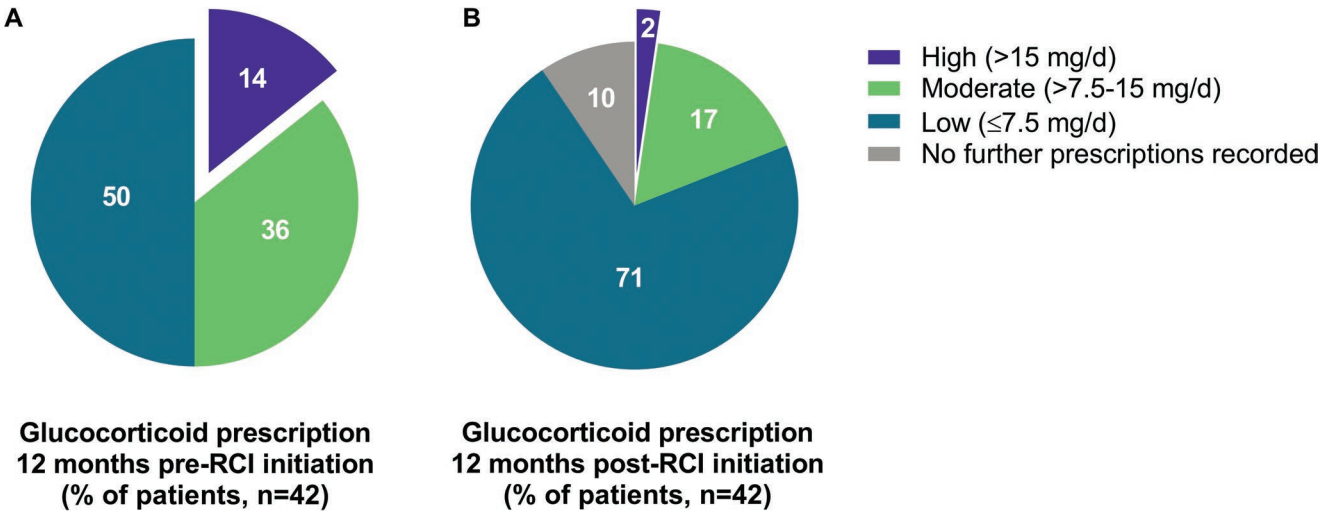
Discussion

This study provides key information about treatment characteristics and clinical disease activity-related outcomes not reported in a previous chart review study, in which RCI was used in patients with RA with a high disease activity who had progressed to second-line or third-line therapies.[20] Our study included a population with refractory disease that is more difficult to treat, as demonstrated by high CDAI and RAPID3 scores, despite these patients being prescribed standard-of-care therapies. Patients also perceived their clinical status as being severe, which was consistent with high TJC and pain VAS scores (Table 3). Our findings are consistent with previous studies that demonstrated the effectiveness of RCI as an adjunctive therapy for short-term administration to manage RA flares because the category 'no longer required' was the main reason RCI was discontinued.[1,4,34] Only a small proportion (4.3%) of patients discontinued RCI due to side effects, but this may be because adverse events are not proactively collected in EMRs. Of note, a patient with a high RA disease activity may have several flares throughout the year, possibly warranting multiple intermittent courses of RCI therapy.

Our study also highlights the importance of recording follow-up disease activity assessments and PROs within the EMR database as outlined by ACR and CMS clinical quality measures guidelines.[35–38] These guidelines recommend at least annual assessments of functional status and clinical disease activity.[35–38] Though not all patients received both a clinical (e.g. CDAI) or functional (e.g. RAPID3) assessment in the 12 months following RCI initiation, most patients were administered one of the two assessments. RAPID3 is a quickly administered and scored assessment of RA disease activity that does not include clinical measures; however, it possibly overestimates disease severity compared to CDAI and Disease Activity Score with 28 joint count and ESR (DAS28-ESR).[39] Patients may be more empowered to manage their disease status and progression if they all received documented quality measures in the form of regular clinical assessments and physician feedback at follow-up visits.

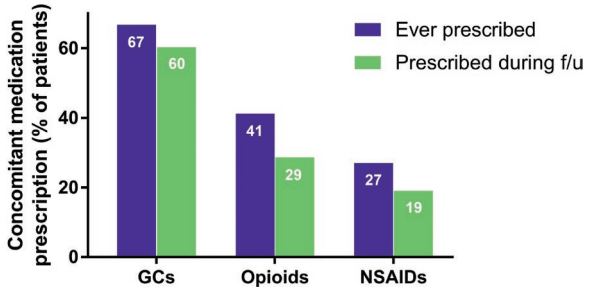
Treatment patterns, medical history and GC dosing are important topics that should be continually discussed by practitioners with patients.[12,20,40,41] Recent ACR guidelines strongly discourage long-term GC use to maintain treatment targets in patients with RA. The European League Against Rheumatism (EULAR) advises GC tapering "as rapidly as clinically possible."[32] RCI treatment is associated with reduction

Figure 3. Proportion of patients prescribed GCs during the 12 months pre-RCI initiation (A) and 12 months post-RCI initiation (B).



GCs, glucocorticoids; RCI, repository corticotropin injection.

Figure 4. Proportion of patients prescribed concomitant medications, including glucocorticoids, NSAIDs and opioids, during the 12 months pre-RCI and post-RCI initiation.



GCs, glucocorticoids; NSAIDs, nonsteroidal anti-inflammatory drugs; f/u, follow-up; RCI, repository corticotropin injection.

of the use of concomitant medications such as GCs and DMARDs.[12,14,18,21,38] In the current study, a larger proportion of patients receiving GCs were prescribed high doses (>15 mg/d) in the 12 months pre-RCI initiation (14%) *versus* at 12 months post-RCI (3%). The analyses performed in this real-world EMR study were unbiased as to dosing of any medications; however, these high GC doses are not recommended for the treatment of RA.[32,42–44] Our results did not show a similar reduction in DMARD prescriptions, possibly because having been recently prescribed DMARDs was necessary for inclusion and/or due to the small sample size. In the 12 months post-RCI initiation, five patients stopped receiving prescriptions for csDMARDs and four patients began receiving prescriptions for tsDMARDs or bDMARDs. It is possible that these four patients with refractory RA did not achieve low disease activity within 12 months post-RCI initiation and thus were prescribed different DMARDs. Regardless, a similar proportion of patients were prescribed DMARDs in the 12 months pre-RCI and post-RCI initiation. Additionally, DMARDs are standard-of-care therapies through the maintenance phase of RA treatment, and we did not expect to see a change in dosing in this real-world study. Pain management with opioids is also a concern, as the prevalence of chronic opioid use amongst patients with RA doubled to 17% between 2002 and 2015.[32] Our study observed reductions in pain medications 12 months post-RCI initiation, which may be indicative of lessened RA flare severity. Patients are less likely to discontinue RCI therapy due to allergic reactions or infections and can tolerate RCI treatment longer when compared to biologics (e.g. infliximab).[16]

Data for RF and anti-CCP were often missing from the EMRs, likely because these procedures are regularly performed once at the time of diagnosis and the average time to diagnosis (6.0±2.8 years) was longer than the evaluation period of EMR data (1–4 years before the RCI initiation visit) for inclusion in the study. A recent study demonstrated that the M05* ICD-10 diagnosis code correlated with serum detection of anti-CCP or RF antibodies with approximately 85% accuracy; therefore, the M05* ICD-10 diagnosis code may be used as a proxy to impute RA seropositivity.[45]

The limitations of this study are mostly related to incomplete data in the EMRs. This retrospective and exploratory study comprised effectiveness assessments, which relied on comparison of outcomes between pre-RCI initiation and 12 months post-RCI initiation in a small subset of patients

with available EMR data. The availability of clinical disease activity measures was limited to CDAI because the EMRs did not contain routine assessments with the DAS28-ESR, which is currently the standard for evaluating RA disease activity. However, CDAI is easier to administer at any time and has been reported to be more effective at evaluating RA remission than DAS28.[30,46] The small subset sample size may not have allowed for detection of changes beyond an MCID threshold. Unlike medical-based and pharmacy-based claims database analyses, in which a continuous enrolment can be defined and treatment patterns can be tracked based on refill patterns, prescription patterns ascertained from EMR data are subject to greater uncertainty. Because linkage to pharmacy claims data was not available, the study assumed that patients filled their prescriptions over the period of observation unless physicians recorded a stop in treatment. Therefore, the categorization of medication use may be underestimated. Inferences based upon the findings described here may be limited to the included population (mostly middle-aged white women), which may constrain generalizations of these results to the larger population with refractory RA. However, this patient demographic is highly represented in both this study and the overall RA population. No comparator arm was included in this real-world study, but controlled comparator studies with other monotherapies are complicated by the fact that RCI is initiated in response to RA flares and high disease activity despite concomitant treatment with first-line therapies (GCs and/or DMARDs). Although this retrospective EMR study cannot directly conclude that RCI is effective in the treatment of refractory RA, as a recent placebo-controlled clinical trial has,[4] in real-world clinical practice we still observed that patients with refractory RA experienced clinical improvements 12 months after initiation with RCI. In future studies, systematic reporting of quality-of-care metrics (CDAI and patient functional assessments) and increased linkage of EMR data to prescription fill data would improve compliance monitoring and effectiveness assessments of RCI treatment.

Despite these limitations, data collected from the Columbus™ repository of EMRs obtained through BendCare, LLC, a large network of rheumatology practices, captured PROs and clinical disease activity assessments, which are data not frequently available in pharmacy or medical claims databases. The treatment patterns identified in our study may provide insights to improve patient care and help better understand practices for RCI use in RA. Similar real-world effectiveness studies have reported positive clinical outcomes after initiating RCI treatment in patients with refractory diseases, including multiple sclerosis,[40,47] sarcoidosis,[12] uveitis,[41] nephrotic syndrome,[48] systemic lupus erythematosus, and dermatomyositis or polymyositis.[20] Outcomes of these studies align with those presented here for RA. In the treatment of refractory sarcoidosis and moderate to severe uveitis, RCI reduced disease severity and concomitant medication use such as GCs.[12,41] Patients with nephrotic syndrome[48] or multiple sclerosis,[40,47] in whom prior immunosuppressive or cytotoxic treatments have failed, also showed reduced disease activity scores after initiation of RCI. These studies, combined with our data for RA, provide strong real-world evidence supporting the clinical effectiveness of RCI across a wide spectrum of inflammatory diseases.

Conclusions

This study suggests that patients with refractory, persistently active RA may benefit from RCI. Most patients in this study were white women older than 50 years, who were prescribed an RCI regimen of 80 units twice weekly for approximately 10 months. This treatment strategy was associated with a decreased number of prescriptions for concomitant medications, including GCs, NSAIDs and opioids, as well as improved disease activity (CDAI) and PROs. These real-world findings are consistent with other well-controlled clinical and observational studies that suggest RCI treatment is safe and effective for patients with refractory RA in routine clinical practice.

Compliance with ethics guidelines

The management of study data conformed to all applicable Health Insurance Portability and Accountability Act rules. All data were de-identified throughout the study to preserve patient anonymity and confidentiality. This observational study was conducted under the research exception provisions of the Privacy Rule, 45 CFR 164.514(e), and was exempt from Institutional Review Board informed consent requirements.

Data availability

The source data for this study are not available to be shared by the authors. The Columbus™ electronic medical system database is a proprietary analytic platform that can be accessed through contract with BendCare, LLC (contact at https://www.bendcare.com).

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Correspondence: George J Wan, Health Economics and Outcomes Research, Mallinckrodt Pharmaceuticals, Hampton, NJ 07921, USA. Email: george.wan@mnk.com

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