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ORIGINAL RESEARCH

Post Hoc Analysis of Predictors of Clinical Response to Repository Corticotropin Injection in Persistently Active Rheumatoid Arthritis

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ABSTRACT

Introduction: A phase IV clinical trial confirmed the safety and efficacy of repository corticotropin injection (RCI, Acthar® Gel) in patients with refractory rheumatoid arthritis (RA) that was nonresponsive to standard-of-care therapies. The objective of this post hoc analysis was to identify baseline demographics and clinical characteristics that may be predictors of response to RCI.

Methods: The phase IV trial was a two-part, randomized, placebo-controlled withdrawal study. Post hoc analysis was conducted with the open-label portion of the trial data, in which all 258 subjects received RCI (80 U) twice weekly for 12 weeks. Responders were subjects who achieved low disease activity (LDA) by a Disease Activity Score with 28-joint count and erythrocyte sedimentation rate (DAS28-ESR) of < 3.2 at week 12. Responders were compared with nonresponders by assessing the proportion of subjects in each group for demographics and clinical characteristics, including weight, disease duration, medical history including osteoarthritis and unrelated joint conditions, hemoglobin A1c, C-reactive protein, ESR, DAS28-ESR, Clinical Disease Activity Index (CDAI), depression, anxiety, tender joint count (TJC), and swollen joint count (SJC). Bivariate analysis followed by multiple logistic regression analysis were conducted to identify significant baseline predictors for the outcome of achieving LDA by week 12.

Results: Bivariate analysis showed that RCI responders had significantly lower baseline TJC ($p = 0.0310$), SJC ($p = 0.0018$), ESR ($p = 0.0487$), and CDAI ($p = 0.0112$) and shorter RA disease duration ($p = 0.0446$). Subjects were less likely to achieve LDA if they had osteoarthritis ($p < 0.0001$), other joint-related conditions unrelated to RA ($p < 0.0001$), anemia ($p = 0.0132$), depression ($p = 0.0006$), or prior or concomitant use of targeted-synthetic or biologic disease-modifying antirheumatic drugs ($p < 0.0001$). Multiple logistic regression analysis revealed that, of the above, only ongoing osteoarthritis ($p = 0.0272$) or other joint-related conditions ($p = 0.0193$) were significant negative predictors of RCI response.

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Conclusions: These results identify specific patient characteristics that may be considered predictors of positive or negative clinical response to RCI.

Keywords: Acthar Gel; Low disease activity; RCI; Repository corticotropin injection; Responders; Rheumatoid arthritis

Key Summary Points

Why carry out this study?

An estimated 6% of patients in the US have persistently active rheumatoid arthritis (RA) inadequately controlled by standard-of-care therapies, such as disease-modifying antirheumatic drugs (DMARDs) and corticosteroids.

This study aimed to establish significant baseline predictors of clinical response to repository corticotropin injection (RCI; Acthar® Gel) in subjects with refractory RA via post hoc analysis of data from a phase IV clinical trial.

What was learned from this study?

Bivariate analysis indicated that subjects were significantly more likely to achieve low disease activity (LDA) with RCI if they had a shorter disease duration, a lower number of swollen or tender joints at baseline, and lower baseline scores for erythrocyte sedimentation rate (ESR) or Clinical Disease Activity Index (CDAI).

Bivariate comparisons indicated that subjects were significantly less likely to achieve LDA with RCI if they had osteoarthritis (OA), other joint-related conditions not related to RA, anemia, depression, or prior or concomitant use of targeted-synthetic or biologic DMARDs.

Logistic regression analysis showed that, of the above, only OA or other joint-related conditions not related to RA are significant negative predictors of RCI response.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that, if left untreated, can lead to bone/cartilage destruction, progressive joint damage, and disability [1]. The worldwide incidence of RA is estimated to be three cases per 10,000 people annually, with a 1% prevalence worldwide [2]. The prevalence of RA increases with age and peaks between 35 and 50 years of age [2].

The primary goal of RA treatment is to achieve remission, or alternatively low disease activity (LDA), following a "treat-to-target" strategy [3]. The cornerstone of RA treatment is disease-modifying antirheumatic drugs (DMARDs), which should be initiated immediately after diagnosis [4, 5]. DMARDs are classified as conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), or targeted-synthetic DMARDs (tsDMARDs) [4, 5]. DMARDs have been demonstrated to suppress inflammation and, in most patients, slow the progression of joint damage [6]. Despite numerous available DMARDs, in the majority of patients, LDA is not achieved or maintained over a prolonged period [6, 7]. An estimated 6% of patients with moderate to severe RA (approximately 30,000–34,000 US patients) do not respond to DMARDs [8–10]. Failure to achieve LDA and possibly remission can lead to irreversible joint damage [6]. One-year remission rates with DMARD treatment show considerable variability, ranging from 13% to 74% [7]. The rate of remission can vary depending on multiple factors including the length of time the patient has RA, the use of monotherapy or combination therapy, the time point assessed, and differing remission or response criteria [6, 7]. During RA flares or changes in DMARD treatment, short courses of corticosteroids are often prescribed to provide rapid control of inflammation and minimize joint damage [3]. However, long-term use of corticosteroids is associated with serious adverse events including bone loss, heart failure, mood disorders, diabetes, and cataracts [11]. In patients with persistently active disease or frequent flares who do not adequately respond to DMARDs and/or

corticosteroids, there is an unmet need for additional treatments that can be effectively utilized.

Repository corticotropin injection (RCI; Acthar® Gel) is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides [12]. RCI has demonstrated anti-inflammatory and immunomodulatory effects by engaging melanocortin receptors (MCRs) 1–5 [13–15]. Traditionally, the effects of RCI have been attributed to activation of MC2R on adrenocortical cells, which stimulates production of endogenous cortisol [16]. However, recent studies have provided evidence that RCI also activates other MCRs found on a variety of cells and directly inhibits proliferation of B cells and antibody production [13–15]. Such steroid-independent effects of RCI contribute to its efficacy in patients who do not adequately respond to corticosteroids in the treatment of other inflammatory autoimmune diseases, such as systemic lupus erythematosus [17].

In a phase IV, multicenter, randomized, placebo-controlled withdrawal study, a Disease Activity Score with 28-joint count and erythrocyte sedimentation rate (DAS28-ESR) LDA was achieved in > 60% of subjects with 12 weeks of open-label RCI therapy [18]. LDA was subsequently maintained in the majority of patients during an additional 12 weeks of RCI treatment [18]. In the placebo group, LDA was maintained with open-label RCI therapy in 42% of subjects for 3 months after discontinuation of RCI [18].

This study aimed to identify predictors of clinical response to RCI in patients with persistently active RA despite treatment with a corticosteroid and 1 or 2 DMARDs via post hoc analysis of data from the phase IV clinical trial described above.

METHODS

Study Design

This study was a post hoc analysis of a phase IV clinical trial previously reported [18]. Part 1 of the clinical trial was open-label, with all subjects receiving RCI therapy (80 U twice weekly) for 12 weeks. Part 2 of the trial was double-blinded, with subjects in whom DAS28-ESR LDA was achieved at week 12 randomly assigned to receive either RCI (80 U) or placebo twice weekly for 12 weeks.

This study was performed in accordance with the ethical principles outlined in the Declaration of Helsinki and its later amendments. 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 post hoc 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. This study is based on a previously performed and published study and does not contain any new human participants.

Subjects

The phase IV clinical study enrolled adults with active RA despite treatment with a stable dose of prednisone (5–10 mg) or prednisone equivalent and 1 or 2 csDMARDs or 1 bDMARD. Active RA was defined as a DAS28-ESR $\geq$ 3.2. Subjects with baseline and part 1 data from the phase IV study were included in the current analyses.

Post Hoc Analysis

Responders were classified according to the definition used in the phase IV clinical study: subjects who achieved a DAS28-ESR < 3.2 at week 12 were considered responders to RCI treatment. Subject demographics and clinical characteristics at treatment initiation were summarized using descriptive statistics, comparing responders and nonresponders using Student's *t* tests, Mann–Whitney *U* tests, Pearson Chi-squared tests, or Fisher's exact tests, as appropriate.

A multiple logistic regression was conducted to identify significant baseline predictors for the outcome of achieving LDA (DAS28-ESR < 3.2) by week 12. The regression model controlled for age (categorical), sex, race/ethnicity, and

disease duration (categorical). Biometrics, clinical characteristics, and treatment patterns determined relevant through bivariate comparison or clinical value were included in the model. Baseline biometrics were body mass index (BMI), hemoglobin A1c (HbA1c), C-reactive protein (CRP), tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), DAS28-ESR, and clinical disease activity index (CDAI). All data were tested for normality using a Shapiro–Wilk test.

Modeling

For the outcome of LDA achievement at week 12, baseline predictive factors were examined with bivariate comparisons by RCI responder group (responder vs. nonresponder). Biometric continuous predictors were selected based on bivariate comparison with a significance level of $p < 0.05$. Multiple logistic regression analysis was performed to identify any significant clinical predictors of achieving LDA with RCI. The model controlled for age, sex, race/ethnicity, comorbidities, and prior or concomitant use of tsDMARDs/bDMARDs at baseline. The model examined issues of multicollinearity of predictors using generalized variance inflation factors (GVIF) to compare covariates across the model, with a cutoff of GVIF > 5, and was adjusted appropriately. All statistical analyses were two-tailed, and significance was determined as $p < 0.05$.

RESULTS

Baseline Demographics and Clinical Characteristics for RCI Response

Baseline demographics for 258 subjects with RA were categorized according to RCI response (Table 1). The majority of patients were Hispanic/Latino (82.6%), with 46.5% residing in Mexico. The mean age of the study population was 51.0 years, with mostly female subjects (89%, $n = 230$). Most demographics were similar between responders and nonresponders; however, approximately 70% of Hispanic/Latino subjects achieved LDA ($n = 213$), while only 34% of White non-Hispanic/Latino ($n = 32$) and 30% of Black/African American non-Hispanic/Latino ($n = 10$) subjects were classified as responders. Age and sex were not predictive of response to RCI therapy.

Baseline clinical characteristics categorized by RCI response are summarized in Table 2. Mean duration of RA was significantly lower in responders (8.8 years) compared to nonresponders (10.9 years, $p = 0.0446$). Significantly more nonresponders compared to responders had a clinical diagnosis of anemia (13.7% vs. 4.3%, respectively, $p = 0.0132$) or depression (16.8% vs. 3.7%, respectively, $p = 0.0006$). Osteoarthritis (OA) was a comorbidity in 1.8% of responders compared to 20% of nonresponders ($p < 0.0001$). Other joint-related conditions unrelated to RA (see Table S1 in the electronic supplementary material for a list of all medical conditions included in this category) were significantly more likely to be a comorbidities of nonresponders compared to responders (32.6% vs. 9.2%, respectively, $p < 0.0001$). Baseline scores for patient-reported outcome measures, including the Patient Assessment of Pain Visual Analogue Scale, Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Work Productivity and Activity Impairment (WPAI), were not significantly different between responders and nonresponders.

Biometric characteristics at baseline were categorized by RCI response and are presented in Table 3. Nonresponders had significantly higher baseline mean values for TJC ($p = 0.0310$), SJC ($p = 0.0018$), ESR ($p = 0.0487$), and CDAI ($p = 0.0112$) compared to RCI responders. A significantly greater proportion of RCI responders had prediabetes (HbA1c $\geq$ 5.7% to < 6.5%) compared with nonresponders ($p = 0.0320$).

Baseline Treatment and RCI Response

Subjects who had prior or concomitant use of csDMARDs were significantly more likely to respond to RCI therapy, whereas those with prior or concomitant use of tsDMARDs/

Table 1 Baseline demographics by LDA responder status at week 12 of RCI treatment

Demographics	Responder mean (SD)/*n* (%)	Nonresponder mean (SD)/*n* (%)	*p* value
Number of subjects	163 (61.2)	95 (36.8)	
Age (years)	50.4 (11.5)	52.0 (13.5)	0.3447
Group, *n* (%)			
18–34 years	15 (9.2)	9 (9.5)	1.0
35–44 years	30 (18.4)	18 (18.9)	1.0
45–54 years	60 (36.8)	26 (27.4)	0.1572
55–64 years	41 (25.2)	23 (24.2)	0.9843
> 65 years	17 (10.4)	19 (20.0)	0.0508
Sex, *n* (%)			
Male	19 (11.7)	9 (9.5)	0.7367
Female	144 (88.3)	86 (90.5)	0.7367
Race/ethnicity, *n* (%)			
Hispanic/Latino	148 (90.8)	65 (68.4)	**< 0.0001**
Non-Hispanic/Latino, White	11 (6.7)	21 (22.1)	**0.0006**
Non-Hispanic/Latino, Black or African American	3 (1.8)	7 (7.4)	0.0410
Non-Hispanic/Latino, other	1 (0.6)	2 (2.1)	0.5566
Country, *n* (%)			
Argentina	17 (10.4)	7 (7.4)	0.5524
Mexico	90 (55.2)	30 (31.6)	**0.0004**
Peru	14 (8.6)	13 (13.7)	0.2807
US/Puerto Rico	42 (25.8)	45 (47.4)	**0.0007**

Independent-samples *t* test with unequal variance assumption was used for continuous variables, and Mann–Whitney *U* test was used for ordinal grouping

LDA low disease activity; *RCI* repository corticotropin injection

Numbers in bold indicate statistical significance of $p < 0.05$

bDMARDs were significantly less likely to respond to RCI (Fig. 1).

Multiple logistic regression was used to predict baseline factors for DAS28-ESR LDA at week 12 of RCI treatment. The logistic regression model included biometrics, clinical characteristics, and treatment patterns deemed relevant from the bivariate comparison or to have clinical value. csDMARDs were excluded from the regression analysis due to the very high proportion of responders and nonresponders using these drugs, such that the statistical significance observed between groups in the bivariate analysis was deemed not to be clinically meaningful. The regression analysis showed that subjects who had ongoing joint-

Table 2 Baseline clinical characteristics by LDA responder status at week 12 of RCI treatment

Clinical characteristics	Responder mean (SD)/*n* (%)	Nonresponder mean (SD)/*n* (%)	*p* value
Disease duration (years)	8.8 (8.0)	10.9 (8.1)	**0.0446**
Group, *n* (%)			
< 2 years	29 (17.8)	11 (11.6)	0.2496
≥ 2 to < 5 years	36 (22.1)	16 (16.8)	0.3943
≥ 5 to < 10 years	44 (27.0)	24 (25.3)	0.8746
≥ 10 years	54 (33.1)	44 (46.3)	**0.0486**
Comorbidities (ongoing), *n* (%)			
Anemia	7 (4.3)	13 (13.7)	**0.0132**
Anxiety	7 (4.3)	6 (6.3)	0.5583
Asthma and reactive lung disease	8 (4.9)	7 (7.4)	0.5900
Depression	6 (3.7)	16 (16.8)	**0.0006**
Hypertension	40 (24.5)	32 (33.7)	0.1511
OA	3 (1.8)	19 (20.0)	< **0.0001**
Joint-related conditions, other (not related to RA)	15 (9.2)	31 (32.6)	< **0.0001**
Rheumatic autoimmune disease	5 (3.1)	7 (7.4)	0.1321
PROMs, mean (SD)			
VAS score	65.7 (19.9)	63.5 (21.2)	0.4048
HAQ-DI score	1.7 (0.6)	1.7 (0.6)	0.8479
FACIT-F score	23.0 (8.4)	22.5 (8.4)	0.6317
WPAI-1 score	64.0 (23.8)	62.4 (24.0)	0.6132

Independent-samples *t* test with unequal variance assumption was used for continuous variables, and Mann–Whitney *U* test was used for ordinal grouping

FACIT-F Functional Assessment of Chronic Illness Therapy-Fatigue; *HAQ-DI* Health Assessment Questionnaire-Disability Index; *LDA* low disease activity; *OA* osteoarthritis; *PROMs* patient-reported outcome measures; *RCI* repository corticotropin injection; *VAS* Visual Analog Scale; *WPAI-1* Work Productivity and Activity Impairment-1

Numbers in bold indicate statistical significance of $p < 0.05$

related conditions unrelated to RA (odds ratio [OR], 0.31; 95% confidence interval [CI], 0.11–0.82; $p = 0.0193$) or ongoing OA (OR, 0.17; 95% CI, 0.03–0.75; $p = 0.0272$) were significantly less likely to achieve LDA by week 12 (Table 4). The logistic regression identified no other variables as positive or negative predictors of response to RCI.

DISCUSSION

Selecting therapies for only those individuals likely to benefit from treatment is important to improve safety and efficacy outcomes for patients, as well as to optimize economic resources [19]. A previous multicenter, prospective RA cohort study found that male sex and younger age, as well as lower BMI,

Table 3 Baseline biometric characteristics by LDA responder status at week 12 of RCI treatment

Biometric characteristics	Responder mean (SD)/*n* (%)	Nonresponder mean (SD)/*n* (%)	*p* value
Weight (kg)	72.0 (15.8)	74.3 (19.0)	0.3330
BMI	28.8 (5.7)	28.8 (5.7)	0.9175
Group, *n* (%)			
Underweight: BMI < 18.5	2 (1.2)	0 (0.0)	0.5329
Normal: 18.5 ≤ BMI < 25.0	38 (23.3)	24 (25.3)	0.8395
Overweight: 25.0 ≤ BMI < 30.0	67 (41.1)	43 (45.3)	0.6024
Obese: BMI ≥ 30.0	56 (34.4)	28 (29.5)	0.5032
HbA1c	5.6 (0.4)	5.5 (0.4)	0.1021
Group, *n* (%)			
Normal: < 5.7%	87 (53.4)	63 (66.3)	0.0572
Prediabetes: ≥ 5.7 to < 6.5%	75 (46.0)	30 (31.6)	**0.0320**
Diabetes: ≥ 6.5%	1 (0.6)	2 (2.1)	0.5566
CRP[a]	17.1 (26.4)	24.3 (40.0)	0.1197
Group, *n* (%)			
≤ 10 mg/L	94 (59.9)	51 (54.3)	0.6227
> 10 to ≤ 30 mg/L	41 (26.1)	24 (25.5)	1.0000
> 30 mg/L	22 (14.0)	19 (20.2)	0.2296
TJC	13.9 (6.9)	15.9 (7.2)	**0.0310**
SJC	10.0 (4.9)	12.3 (5.9)	**0.0018**
ESR	41.2 (22.4)	47.9 (28.1)	**0.0487**
Group, *n* (%)			
≤ 25 mg/h	54 (33.2)	23 (24.2)	0.1710
> 25 to ≤ 45 mg/h	49 (30.1)	26 (27.4)	0.7510
> 45 mg/h	60 (36.8)	46 (48.4)	0.0897
DAS28-ESR	6.2 (1.0)	6.5 (1.0)	0.0822
Group, *n* (%)			
> 3.2 to < 5.1 (reference)	17 (10.4)	8 (8.4)	0.7582
≥ 5.1	146 (89.6)	87 (91.6)	0.7582

Table 3 continued

Biometric characteristics	Responder mean (SD)/*n* (%)	Nonresponder mean (SD)/*n* (%)	*p* value
CDAI	36.8 (11.9)	40.9 (12.7)	**0.0112**

[a]CRP variable had $n = 157$ for the responder group and $n = 94$ for the nonresponder group

BMI body mass index; *CDAI* Clinical Disease Activity Index; *CRP* C-reactive protein; *DAS28-ESR* Disease Activity Score with 28-joint count and erythrocyte sedimentation rate; *ESR* erythrocyte sedimentation rate; *HbA1c* hemoglobin A1c; *LDA* low disease activity; *RCI* repository corticotropin injection, *SJC* swollen joint count; *TJC* total joint count

Independent-samples *t* test with unequal variance assumption was used for continuous variables, and Mann–Whitney *U* test was used for ordinal grouping

Numbers in bold indicate statistical significance of $p < 0.05$

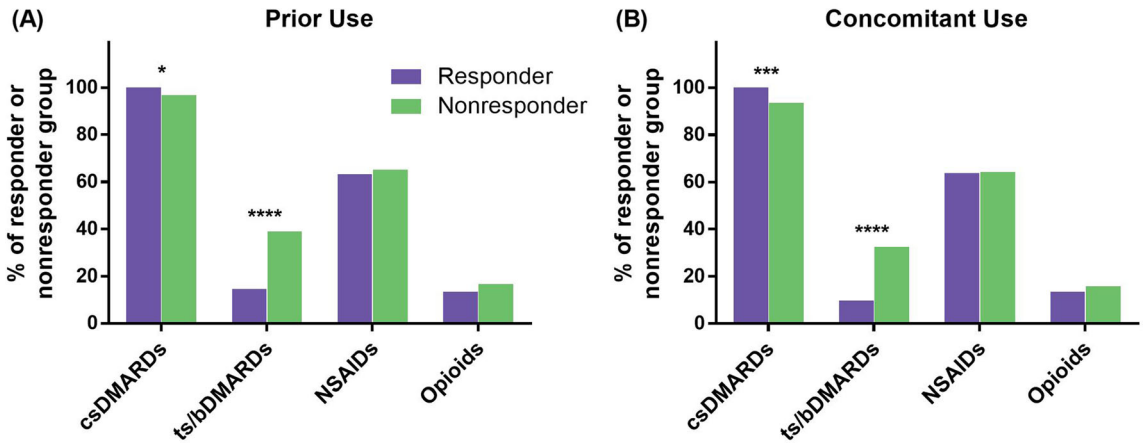

Fig. 1 Baseline treatment by drug class categorized by responder or nonresponder status at week 12 of RCI treatment. **A** Prior use to index date. **B** Concomitant use during open-label period through week 12. Difference in group frequency determined using Chi-square or Fisher's exact test with $\alpha = 0.05$, $^{*}p < 0.05$, $^{***}p < 0.001$, and $^{****}p < 0.0001$. *csDMARDs* indicates conventional synthetic DMARDs; *DMARDs* disease-modifying antirheumatic drugs; *ts/bDMARDs* targeted-synthetic/biologic DMARDs; *NSAIDs* nonsteroidal anti-inflammatory drugs

comorbidity index, or HAQ-DI score were independent factors associated with achieving LDA in subjects with RA after DMARD treatment [20]. The same study found that 43% of subjects did not achieve LDA. This was most common in subjects treated with glucocorticoids or more than two DMARDs, suggesting that these patients had difficult to treat refractory RA [20].

In our study, individuals with a shorter RA disease duration (< 10 years) were more likely to achieve LDA in response to treatment with RCI; this is also a known factor in predicting the response of a patient with RA to methotrexate [21]. Subjects who had lower SJC, TJC, ESR, or CDAI scores were also more likely to be responders to RCI therapy. However, disease duration, SJC, TJC, ESR, and CDAI were found not to be significant predictors in the logistic regression analysis. Similarly, patients with a lower number of swollen or tender joints have been reported to be more responsive to anti–tumor necrosis factor therapy [22]. Our study found no difference between the male and female responder rate to RCI therapy, whereas previous studies have suggested that more males than females treated with standard-of-care RA therapies achieve LDA [20, 22].

Subjects with OA, other joint-related conditions unrelated to RA, anemia, depression, or prior or concomitant use of tsDMARDs/bDMARDs were significantly less likely to

Table 4 Multiple logistic regression of DAS28-ESR LDA at week 12 of RCI treatment

Predictors (at baseline)	Estimate (β)	Standard error	Odds ratio	95% CI	p value
Disease duration					
$\geq$ 10 years (reference)					
$<$ 2 years	0.6	0.5	1.73	0.65–4.84	0.2777
$\geq$ 2 to $<$ 5 years	0.2	0.5	1.26	0.53–3.12	0.6081
$\geq$ 5 to $<$ 10 years	0.2	0.4	1.24	0.56–2.78	0.5929
Biometrics					
HbA1c	0.6	0.4	1.92	0.86–4.43	0.1179
CRP	0.0	0.0	0.99	0.98–1.00	0.0987
ESR	0.0	0.0	0.99	0.98–1.01	0.3761
TJC[a]	0.0	0.0	0.98	0.93–1.04	0.5418
SJC[a]	0.0	0.0	0.98	0.91–1.06	0.5619
PROMs and clinical assessments					
Pain VAS	0.0	0.0	1.01	0.99–1.03	0.3686
FACIT-F	0.0	0.0	1.02	0.97–1.06	0.4767
WPAI	0.0	0.0	1.00	0.99–1.02	0.7361
CDAI[a]	0.0	0.0	0.98	0.95–1.01	0.2036
Comorbidities					
Asthma and reactive lung disease (ongoing)	1.4	0.9	4.16	0.80–25.89	0.0906
Depression	– 0.5	0.8	0.62	0.12–2.88	0.5452
Hypertension (ongoing)	– 0.4	0.4	0.68	0.30–1.55	0.3922
OA (ongoing)	– 1.8	0.8	0.17	0.03–0.75	**0.0272**
Joint-related conditions, other (not related to RA; ongoing)	– 1.2	0.5	0.31	0.11–0.82	**0.0193**
Treatment patterns					
ts/bDMARDs (prior use)	0.7	0.8	1.97	0.43–10.75	0.3981

Table 4 continued

Predictors (at baseline)	Estimate (β)	Standard error	Odds ratio	95% CI	p value
ts/bDMARDs (concomitant use)	− 1.5	0.9	0.22	0.04–1.12	0.0773

[a]CDAI is highly correlated with tender and swollen joint counts, resulting in multicollinearity

BMI body mass index; *CDAI* Clinical Disease Activity Index; *CI* confidence interval; *CRP* C-reactive protein; *DAS28-ESR* Disease Activity Score with 28-joint count and erythrocyte sedimentation rate; *ESR* erythrocyte sedimentation rate; *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue; *HAQ-DI* Health Assessment Questionnaire-Disability Index; *HbA1c* hemoglobin A1c; *LDA* low disease activity; *OA* osteoarthritis; *PROMs* patient-reported outcome measures; *RCI* repository corticotropin injection; *SJC* swollen joint count; *TJC* total joint count; *ts/bDMARDs* targeted-synthetic or biologic disease-modifying antirheumatic drugs; *VAS* visual assessment score; *WPAI-1* Work Productivity and Activity Impairment-1

CDAI has been estimated using a separate model with all covariates, excluding tender/swollen joint count. Using either CDAI or tender/swollen joint counts in the model did not significantly impact the estimates for all other predictors

Numbers in bold indicate statistical significance of $p < 0.05$

respond to RCI in the bivariate analysis. However, in the logistic regression analysis, controlling for other relevant covariates, only OA and other joint-related conditions were significant negative predictors of RCI response. OA and other joint-related conditions, such as back pain, carpal tunnel syndrome, and knee replacement, as described in Table S1, were noted in the patient history of the case report form without protocol-defined criteria for the diagnosis. Non-inflammatory OA joints, caused by joint injury or malalignment instead of by an inflammatory autoimmune disorder like RA, are unlikely to respond to treatment with RCI. When assessing RA disease activity, it is important for the practitioner to differentiate non-inflammatory from inflammatory tender joints found upon examination. Tender joints due to OA rather than to RA are highly likely to be unresponsive to advanced anti-inflammatory therapy such as RCI. If they are scored as inflammatory joints, this will inflate disease activity scores and confuse whether the patient has reached a therapeutic goal such as achievement of LDA. As an example, a patient who presents with nine tender joints (six of which are due to OA, not RA), 0 swollen joints, an ESR of 10, and Patient and Physician Global Assessment scores of 2 has a DAS28-ESR score of 3.57 and a CDAI score of 13, both indicating moderate disease activity. If the same patient has only three tender joints (with no tender joints due to OA), the DAS28-ESR and CDAI scores are 2.86 and 7, respectively, indicating LDA. For this reason, differentiation between joint symptoms caused by active RA and those attributable to OA or other joint-related causes is important. The presence of unresponsive tender joints caused by non-inflammatory OA may incorrectly suggest that a patient did not achieve LDA by either of these metrics when they otherwise would have [23, 24]. Thus, inclusion of these potentially nonresponsive subjects with OA or other joint-related conditions, in whom the joint assessor cannot distinguish joint symptoms due to RA rather than OA or other joint-related conditions, should be considered when designing and conducting future RA trials, as these patients may well confound efficacy results.

During our study, we performed sensitivity analyses to remove patients with OA and other joint-related conditions not related to RA, independently and combined, from the logistic regression. Removal of only patients with OA from the model resulted in concomitant use of tsDMARDs/bDMARDs as a significant negative predictor of achieving LDA (OR, 0.12; 95% CI, 0.01–0.81; $p = 0.0434$) with the largest standardized regression coefficient of the covariates included, classified as the strongest predictor in the model. When patients with other ongoing

joint-related conditions were removed alone or in combination with patients with OA, HbA1c and CRP were significant positive and negative predictors of response, respectively. However, removal of patients with other joint-related conditions, while holding other covariates constant, resulted in a model with a nonsignificant goodness-of-fit and inconclusive predictive power of the individual predictors. The results of this sensitivity analysis are speculative and subject to bias, so we have refrained from drawing any conclusions from them.

The major limitation in our study was that > 80% of all subjects were of Hispanic/Latino ethnicity and lived in Central or South America. This is an important consideration in understanding the implications of this post hoc analysis. In a study of 498 ethnically diverse adults with RA, there was significant variation among different ethnicities, with Hispanic/Latino patients having higher disease activity compared with Caucasian patients [25]. Because the majority of subjects in our study were of Hispanic/Latino ethnicity, and mostly from Mexico, some portion of the observed effects may be due to differential or limited access to medical care prior to enrollment. Furthermore, because this trial may have been the best source of care for some of these patients, a greater placebo effect may have occurred. This population of patients may limit extrapolation of the results to other ethnicities or patients outside of Mexico and Latin America. A recent systematic review found that out of 126 randomized clinical trials for RA, only 4.4% included Hispanic subjects; therefore, it is not clear whether the results would have been similar if the study were conducted in a more diverse population of patients with RA [26].

CONCLUSIONS

This post hoc analysis of a phase IV clinical trial identified a set of clinical and biometric characteristics that predicted which patients with RA are most likely to respond to RCI therapy. Bivariate analysis showed that positive predictors of RCI response were shorter disease duration, lower baseline number of swollen or tender joints, and lower baseline ESR or CDAI scores, while negative predictors of RCI response were concomitant use of tsDMARDs/bDMARDs, anemia, depression, OA, or other joint-related disorders not related to RA. Importantly, logistic regression analysis demonstrated that OA or other joint-related disorders are significant negative predictors of achieving LDA with RCI treatment. These analyses suggest that careful attention should be paid to distinguishing joint tenderness due to OA or other joint-related conditions from RA. Future prospective studies should be conducted to further assess the efficacy of RCI with consideration of such possible confounding factors.

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Compliance with Ethics Guidelines. This study was performed in accordance with the ethical principles outlined in the Declaration of Helsinki and its later amendments. 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 post hoc 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. This study is based on a previously performed and published study and does not contain any new human participants.

Data Availability. The data sets generated and/or analyzed during the current study are available from Kyle.Hayes@mnk.com on reasonable request.

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