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REVIEW

Pain and Fatigue Improvements in Patients Treated with Repository Corticotropin Injection Across Five Indications: A Narrative Review

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ABSTRACT

Repository corticotropin injection (RCI; Acthar® Gel) is approved by the US Food and Drug Administration (FDA) for use in 19 indications, including for the treatment of selected patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), symptomatic sarcoidosis, uveitis, and keratitis. Despite treatment with disease-modifying antirheumatic drugs, many patients with RA, SLE, and other chronic inflammatory rheumatic diseases continue to be affected by severe pain and fatigue, indicating a need for other therapies. To examine the clinical data regarding the impact of RCI treatment on pain and fatigue in selected populations, this review included English-language peer-reviewed publications of clinical trials of any size and cohort studies with more than 10 patients that included pain and/or fatigue based on patient-reported outcomes (PROs) and/or physician-assessed measures in adults following treatment with RCI for RA, SLE, symptomatic sarcoidosis, uveitis, or keratitis. Literature searches identified eight studies that met these criteria. Four studies (reported in five publications) were in patients with RA or SLE, two in patients with sarcoidosis, one in patients with uveitis, and one in patients with noninfectious keratitis. Across the different types of studies assessed (clinical trials, chart reviews, real-world evidence), the results were consistent with respect to the impact of RCI treatment on improving pain and fatigue. As summarized in this review, data from patient- and physician-reported outcome measures in eight studies demonstrate that, in addition to improving more traditional efficacy measures, RCI may also improve pain and fatigue in patients with RA, SLE, symptomatic sarcoidosis, uveitis, and noninfectious keratitis.

PLAIN LANGUAGE SUMMARY

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are chronic autoimmune diseases. Clinical studies of drugs for these diseases do not often ask patients how they feel after treatment. Despite treatment, many people with these diseases have pain and feel tired. Repository corticotropin injection (RCI) is a prescription drug for patients with RA, SLE, and other chronic immune diseases. We reviewed the results of published studies with data on pain and fatigue from patients treated with RCI. Four studies were in patients with RA or SLE. Two studies were in

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patients with symptomatic sarcoidosis. One study was in patients with uveitis. One study was in patients with noninfectious keratitis. These eight studies show that adding RCI to standard treatment lowers pain and fatigue in some patients. It would be helpful to measure pain and fatigue in future clinical studies of drugs for patients with chronic immune diseases.

Keywords: Acthar® Gel; Fatigue; Keratitis; Pain; RCI; Repository corticotropin injection; Rheumatoid arthritis; Sarcoidosis; Systemic lupus erythematosus; Uveitis

Key Summary Points

Why carry out this study?
Despite use of disease-modifying antirheumatic drug (DMARD) therapy, many patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and other chronic immune-mediated diseases continue to be affected by severe pain and fatigue
Results from several clinical trials support the use of repository corticotropin injection (RCI) as treatment for patients with RA, SLE, sarcoidosis, and noninfectious keratitis
This narrative review examines the clinical data on the impact of RCI treatment on pain and fatigue in patients with RA, SLE, symptomatic sarcoidosis, uveitis, and keratitis
What was learned from the study?
Across various studies, treatment with RCI was associated with improvements in patient- and physician-assessed pain and fatigue outcomes in patients with RA, SLE, symptomatic sarcoidosis, uveitis, and noninfectious keratitis
Pain and fatigue are important measures to consider for inclusion alongside conventional efficacy assessments in future clinical trials

INTRODUCTION

Despite use of disease-modifying antirheumatic drug (DMARD) therapy, many patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and other chronic immune-mediated diseases continue to be affected by severe pain and fatigue [1–7]. Other therapies are needed to alleviate the high burden of pain and fatigue experienced by these patients despite treatment with biologics.

Repository corticotropin injection (RCI; Acthar® Gel) is a naturally sourced mixture of adrenocorticotropic hormone analogues and other pituitary peptides. RCI is approved by the US Food and Drug Administration (FDA) for use in 19 indications, including for the treatment of selected patients with RA, SLE, keratitis, uveitis, and symptomatic sarcoidosis [8]. Results from several clinical trials support the use of RCI as treatment for patients with RA, SLE, sarcoidosis, and noninfectious keratitis [9–16]. A prospective, single-group open-label study of RCI in eight patients with refractory RA reported statistically significant improvements in the primary endpoints of Ritchie–Camp articular index tender joint count and swollen joint count and in the total disease activity score for RA (DAS28) at 12 weeks; patient and physician global visual analog scales (VASs) also showed significant improvement at 12 weeks [9]. A prospective single-group study of RCI reported that 67% of patients with active RA and inadequate response to conventional disease-modifying antirheumatic drug (cDMARD) and at least three biologic DMARDs (bDMARDs) met the primary endpoint of adequate response, defined as greater than 1.2 point reduction in DAS28 with C-reactive protein (DAS28-CRP) at 12 weeks compared with baseline [10]. In a randomized, placebo-controlled withdrawal trial of RCI, 259 adults with active RA were treated with open-label RCI for 12 weeks; patients who had achieved low disease activity (LDA) were then randomized to RCI or placebo twice weekly for a 12-week double-blind period [11]. At the end of the double-blind period (24 weeks), 61.0% of patients in the RCI group versus 42.1% in the placebo group ($P = 0.019$)

maintained DAS28-ESR LDA (i.e., less than 3.2); similarly, 85.7% of patients in the RCI group versus 65.8% in the placebo group maintained Clinical Disease Activity Index (CDAI) LDA (i.e., less than or equal to 10) ($P = 0.004$).

A randomized double-blind trial of RCI versus placebo in 169 patients with active SLE and moderate to severe rash and/or arthritis by British Isles Lupus Assessment Group (BILAG)-2004 showed significant improvements in clinically important secondary endpoints of change from baseline to week 16 in 28 swollen joint count/tender joint count and cutaneous lupus erythematosus disease area and severity index (CLASI)-Activity scores [14]. According to post hoc analyses, patients treated with RCI were more likely than patients who had received placebo to achieve BILAG-based combined lupus assessment (BICLA) at weeks 4, 12, and 20. Also, RCI-treated patients with baseline SLEDAI-2 K $\geq$ 10 and CLASI-Activity $\geq$ 11 had greater SRI-4 responses. These results support the utility of RCI for treating patients with persistently active SLE. Patients with higher levels of SLE disease activity appeared to benefit the most from RCI.

Similarly, a randomized comparison of two RCI doses in patients with chronic pulmonary sarcoidosis who were receiving prednisone found significant decreases from baseline in prednisone dosage and improvements in pulmonary function, chest imaging, health-related quality of life, and fatigue for the 16 patients who persisted with 24 weeks of RCI treatment [15]. A prospective, open-label, single-arm phase 4 trial in patients with noninfectious keratitis reported that at week 12 of RCI therapy, 50% of patients had clinically important improvements in the primary endpoint, which was defined as the proportion of patients with at least a 12-point improvement in the symptom bother domain of the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire at week 12 [16].

Real-world experience with RCI has been reported in case series in patients with psoriatic arthritis and SLE [17, 18]; in retrospective chart reviews in patients with sarcoidosis, RA, various rheumatologic diseases, uveitis, SLE, and dermatomyositis/polymyositis (DM/PM) [7, 19–22]; and in claims database analyses in patients with RA, other rheumatologic conditions, and SLE [23, 24]. These types of studies show that in routine clinical practice, patients who receive RCI tend to have difficult-to-treat disease and have tried multiple available alternative treatments without successful resolution of symptoms.

The purpose of this narrative review is to summarize the published clinical data regarding the impact of RCI treatment on pain and fatigue in patients with RA, SLE, symptomatic sarcoidosis, uveitis, and keratitis and to describe characteristics of patients who might benefit from RCI treatment.

METHODS

To identify relevant studies published in peer-reviewed journals, we searched PubMed, BIOSIS Previews, International Pharmaceutical Abstracts, Current Contents, and Embase with the terms "repository corticotropin injection" OR "ACTHAR Gel." This literature review included English-language, peer-reviewed, published research reports of prospective clinical trials of any size and cohort studies (prospective and retrospective) with more than 10 patients that had patient-reported outcomes (PROs) and/or physician-assessed measures related to pain and/or fatigue in adults following treatment with RCI for RA, SLE, symptomatic sarcoidosis, uveitis, or keratitis. We excluded studies written in languages other than English, case reports and case series with 10 or fewer patients, as well as studies published only as abstracts presented at conferences.

Data from the studies that met the inclusion criteria were extracted using a standardized form and summarized in the tables included in this manuscript. This article is based on previously conducted studies and does not involve any new studies in humans or animals performed by any of the authors.

RESULTS

Reviewed Literature

Our literature searches identified eight studies that have published patient- or physician-reported data on pain or fatigue outcomes following treatment with RCI in patients with RA, SLE, symptomatic sarcoidosis, uveitis, and noninfectious keratitis. The findings from these studies are summarized below and in Tables 1, 2, and 3.

PRO tools used in the studies summarized in this report include the functional assessment of chronic illness therapy-fatigue (FACIT-F) [11, 12]; the lupus quality of life (LupusQOL) instrument, which includes pain-specific and fatigue-specific domains [25]; the fatigue assessment scale (FAS) [15]; patient assessment of pain by VAS (VAS pain) [22, 26]; and for uveitis and keratitis, the ocular discomfort score (ODS) [16]; four-symptom questionnaire (assessing dryness, grittiness, burning, stinging) [16]; and eye-specific VAS measures (assessing eye dryness, burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, pain) [16]. Burning and stinging may be considered indicators of pain in patients with keratitis. Some studies captured pain and fatigue as a subset of other outcome measures such as change in patients' overall health after RCI initiation (e.g., overall symptoms; lung function; inflammation; QOL; fatigue) [27] and physicians' assessments of patient's status and type of improvement observed after RCI treatment (i.e., improvements in vision, pain, vitreous haze, vitreous flare, and macular edema as well as reduction in background medication use) [21].

Impact of RCI on Pain and Fatigue in RA and SLE

Four studies (reported in five publications) included findings on PRO pain or fatigue measures in patients with RA or SLE (Table 1) [11, 12, 22, 25, 26]. Fleischmann et al. [11] used the patient-reported FACIT-F instrument to measure fatigue at baseline and at days 14 and 28 of treatment as part of a randomized withdrawal study of RCI compared with placebo. The study included 259 patients with active RA despite treatment with a stable dose of prednisone (or an equivalent) and one or two conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or one biologic DMARD (bDMARD). The study consisted of a 12-week open-label period with all patients ($n = 259$) receiving RCI (80 U) twice per week, followed by a 12-week double-blind placebo controlled comparator arm of RCI (80 U) twice per week for patients who had achieved LDA (DAS28-ESR score < 3.2) during the open-label portion ($n = 77$ for each cohort). The enrolled patients (median age, 51 years) were predominantly women (89%), with a mean DAS28-ESR of 6.3, well above the > 5.1 American College of Rheumatology (ACR) threshold for high disease activity [29]. Most patients were being concomitantly treated with methotrexate (96%) and with a nonbiologic DMARD (86%). During the 12-week RCI open-label period, mean FACIT-F scores significantly decreased from baseline to weeks 4, 8, and 12 (all $P < 0.001$). During the double-blind period, patients in both the RCI and placebo groups generally maintained improvements in FACIT-fatigue, with no statistically significant differences between the groups. Post hoc PRO analyses from the same trial showed significantly greater improvements ($P < 0.0001$) in patient-reported pain VAS and FACIT-F from baseline through week 12 among RCI responders (DAS28-ESR score < 3.2) compared with nonresponders in the open-label RCI treatment period [26]. Furthermore, in multivariable linear regression analyses, improvements from baseline in patient-reported pain VAS and FACIT-F correlated with significant decreases in total joint count, DAS28-ESR, and clinical disease activity index (CDAI).

A retrospective electronic medical record (EMR) analysis by Hayes et al. [22] used the US United Rheumatology-Normal Integrated Community Evidence (UR-NICE^{TM}) database to assess the real-world experience of 114 patients with RA during the unit of analysis is days before (pre-index) and after (post-index) RCI initiation. The UR-NICE^{TM} database includes

Table 1 Studies with pain and/or fatigue outcomes following RCI treatment in patients with RA and SLE

Study	Objective, design, and treatment	Outcomes and sample size	Key inclusion/exclusion criteria	Patient baseline characteristics	Fatigue outcomes	Pain outcomes
RA						
Fleischmann et al., 2020 [11]	*Objective:* To assess efficacy, safety, and tolerability of RCI in patients with active RA despite treatment with prednisone (or equivalent) and 1 or 2 csDMARDs or 1 bDMARD *Design:* Randomized, placebo-controlled withdrawal study *Treatment:* Open-label RCI (80 U) twice per week for 12 weeks; patients who achieved LDA (i.e., DAS28-ESR < 3.2) at week 12 were randomized to RCI (80 U) or placebo twice per week during 12-week double-blind period	*Primary endpoint:* Proportion of patients who achieved DAS28-ESR < 3.2 at week 12 in part 1 of study (open-label part) *Fatigue and/or pain outcome(s):* FACIT-fatigue *No. of patients:* Enrolled (N = 259); completed the open-label part (n = 235); achieved LDA at week 12 (n = 163); randomized to RCI (n = 77) and placebo (n = 77); completed the randomized part (RCI, n = 71; placebo n = 56)	*Inclusion:* Age ≥ 18 years; met 2010 ACR/EULAR criteria for active RA (DAS28-ESR > 3.2), despite treatment with a stable dose of prednisone (or equivalent) and 1 or 2 csDMARDs or 1 bDMARD *Exclusion:* Any rheumatic autoimmune disease or inflammatory joint disease other than RA	All enrolled patients: Mean age ± SD 51 ± 12 years Gender: female (89%); male (11%) Methotrexate use: Prior (98%); concomitant (96%) Most common concomitant DMARD type: Nonbiologic (86%); biologic (17%) Mean DAS28-ESR ± SD 6.3 ± 1.0	Open-label period: Mean FACIT-F scores: baseline, 22.8; week 4, 17.8 (vs baseline: P < 0.001); week 8, 16.2 (vs baseline: P < 0.001); week 12, 13.9 (vs baseline: P < 0.001) Double-blind period: Improvement on FACIT-F generally maintained in both groups throughout double-blind period No significant differences RCI vs placebo	None
Hayes et al., 2021 [22]	*Objective:* To describe the demographic and clinical characteristics of patients treated with RCI for RA; describe treatment patterns including prior and/or current medication used to control RA; assess changes in clinical outcomes, laboratory-based disease activity measures, and PROs after RCI initiation *Design:* EMR data analysis *Treatment:* RCI real-world use No. of RCI prescriptions (% patients): 1 (54.4%); ≥ 2 (45.7%); ≥ 5 (10.5%) Of patients with ≥ 2 RCI prescriptions: Mean ± SD 152 ± 117 days from RCI start to last RCI prescription	*Primary endpoint:* No predefined primary endpoint/outcome *Fatigue and/or pain outcomes:* Pain VAS *No. of patients:* N = 114	*Inclusion:* Prescribed RCI between December 6, 2013, and June 5, 2019; no evidence of prior RCI use: ≥ 1 diagnosis of RA at any time before index date; > 1 record with any activity (diagnosis, medication, procedure, biometric) in database > 180 days before and > 180 days after index date *Exclusion:* Not reported	Mean age ± SD 60.1 ± 11.0 years Sex, %: female (81%); male (19%) DMARD, % patients: Any (96%): bDMARDs (74%); csDMARDs (68%); tsDMARDs (15%); ntDMARDs (13%) Other treatments, %: Glucocorticoids (92%); NSAIDs (68%); opioids (59%) CDAI, mean ± SD, 29.7 ± 16.4 (high activity range is 22.1–76.0 according to Aletaha et al., 2005 [28] and Singh et al., 2016 [29])	None	Pain VAS (mean ± SD): Index ± 7 days (6.7 ± 2.4); postindex (5.6 ± 2.9); (mean ± SD decrease −1.1 ± 2.8; P = 0.0056); MCID for pain VAS is 0.5–1.1 according to Wolfe et al., 2007 [30]

Table 1 continued

Study	Objective, design, and treatment	Outcomes and sample size	Key inclusion/exclusion criteria	Patient baseline characteristics	Fatigue outcomes	Pain outcomes
Fleischmann et al., 2021 [26]	*Objective:* To determine the correlation between the clinical response to RCI treatment and improvements in PROs *Design:* Post hoc analysis of randomized, placebo-controlled withdrawal study listed above at Fleischmann et al., 2020 [11] *Treatment:* See above Fleischmann et al., 2020 [31]	*Primary endpoint:* None in post hoc analysis; see above, Fleischmann et al., 2020 [11] *Fatigue and/or pain outcome(s):* Pain-VAS with MCID threshold indicating improvement ≥ 10 mm decrease [30, 32]; FACIT-F with MCID ≥ 3-point decrease [33] No. of patients: Enrolled (N = 259); completed the open-label part (n = 235); achieved LDA at week 12 (n = 163)	*Inclusion:* See entry above for above at Fleischmann et al., 2020 [11] *Exclusion:* See entry above for above at Fleischmann et al., 2020 [11]	See above, Fleischmann et al., 2020 [11]	Mean change from baseline to week 12 in FACIT-F: Responder (n = 160) −10.3 (95% CI −11.6 to −9.0) vs nonresponder (n = 78) −5.3 (95% CI −6.7 to −3.9); $P < 0.0001$ By multivariable linear regression analysis: Change from baseline values in FACIT-F correlated with significant decreases in TJC, DAS28-ESR, and CDAI	Mean change from baseline to week 12 in pain VAS: Responder (n = 163) −47.3 (95% CI −50.8 to −43.8) vs nonresponder (n = 95) −20.3 (95% CI −25.5 to −15.1); $P < 0.0001$ By multivariable linear regression analysis: Change from baseline values in pain VAS correlated with significant decreases in TJC, DAS28-ESR, and CDAI
SLE						
Fiechtner and Montroy, 2014 [12]	*Objective:* To examine the efficacy and safety of RCI for reducing severity of active flares in patients receiving conventional SLE treatment regimens *Design:* Prospective, open-label, phase 4 trial *Treatment:* 80 U daily for 10 days with optional 5-day rescue period for partial or nonresponders	*Primary endpoint:* Changes in baseline in SLEDAI-2 K score to month 3 and month 6 *Fatigue and/or pain outcome(s):* FACIT-fatigue *No. of patients:* N = 10	*Inclusion:* Age 18–75 years; met ACR criteria for SLE; chronic, moderately-to-severely active disease; disease flare while receiving standard treatment for SLE *Exclusion:* Receiving new oral prednisone therapy or change in current oral prednisone dose	Mean age 49 years Sex: female (100%) Mean SLEDAI-2 K: 10	Mean FACIT-F (comparisons vs baseline): Baseline (30.7); day 14 (20.0; $P < 0.01$); day 28 (20.5; $P < 0.01$)	None

Table 1 continued

Study	Objective, design, and treatment	Outcomes and sample size	Key inclusion/exclusion criteria	Patient baseline characteristics	Fatigue outcomes	Pain outcomes
Askanase et al., 2021 [25]	*Objective:* To analyze PRO results and report post hoc analyses to further characterize RCI-dependent effects on QOL and work productivity in patients with higher disease activity *Design:* Secondary and post hoc analyses of Askanase et al. 2020 [14] Randomized, double-blind placebo-controlled trial *Treatment:* RCI or placebo: 80 U every other day through week 4, then twice per week for 20 more weeks (total 24 weeks)	*Primary endpoints:* Proportion of patients who achieved SRI-4 response (4-point reduction from baseline in SLEDAI-2 K, with no new BILAG A score and ≤ 1 new BILAG B organ domain score compared with baseline, and with ≤ 10% increase from baseline in PGA) at week 16 *Fatigue and/or pain outcome(s):* Change from baseline to week 24 in Lupus QOL and WPAI-Lupus questionnaire *No. of patients:* $N = 169$	*Inclusion:* Age ≥ 18 years; active SLE; SLEDAI-2 K score ≥ 6 at screening; clinical SLEDAI-2 K score ≥ 4 at both screening and randomization; moderate to severe rash and/or arthritis by BILAG-2004 *Exclusion:* Severe active lupus nephritis; active CNS lupus ≤ 3 months of screening or between screening and first dose of study drug	Mean age 39.7 years Gender, %: female (92%); male (8%) Mean SLEDAI-2 K score: 9.9 Mean prednisone or equivalent dose 11.1 mg; 95% of patients were receiving ≤ 20 mg daily	None	LupusQOL:[a] Mean ± SD from baseline in pain domain (RCI vs placebo: week 8 (17.6 ± 24.8 vs 12.2 ± 24.4; P = NS); week 16 (20.6 ± 23.8 vs 12.4 ± 24.1; $P < 0.05$); week 24 (22.4 ± 25.9 vs 15.7 ± 26.3; P = NS) Mean ± SD from baseline in fatigue domain (RCI vs placebo: week 8 (10.5 ± 19.4 vs 11.8 ± 24.0; P = NS); week 16 (12.9 ± 25.9 vs 9.0 ± 24.0; P = NS); week 24 (15.9 ± 25.2 vs 10.1 ± 27.3; P = NS) Post hoc analyses of RCI vs placebo: RCI group had greater improvements from baseline in pain domain in patients with higher disease activity scores (i.e., SLEDAI-2 K ≥ 10 at week 16, CLASI-Activity ≥ 11 and BILAG-2004 ≥ 20 at week 24, and BICLA responders at week 16); and in fatigue domain in patients with SLEDAI-2 K ≥ 10 and CLASI-Activity ≥ 11 at week 16

ACR American College of Rheumatology, *bDMARD* biologic disease-modifying antirheumatic drug, *BICLA* BILAG-based combined lupus assessment, *BILAG* British Isles Lupus Assessment Group, *CDAI* clinical disease activity index, *CNS* central nervous system, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28* disease activity score for RA, *DM/PM* dermatomyositis/polymyositis, *EMR* electronic medical record, *ESR* erythrocyte sedimentation rate, *EULAR* European League Against Rheumatism, *FACIT-F* functional assessment of chronic illness therapy-fatigue, *HAQ* health assessment questionnaire, *MCID* minimum clinically important difference, *LDA* low disease activity, *NS* not significant, *NSAIDs* nonsteroidal anti-inflammatory drugs, *ntDMARD* nontraditional disease-modifying antirheumatic drug, *PGA* physician global assessment, *PRO* patient-reported outcome, *QOL* quality of life, *RA* rheumatoid arthritis, *RCI* repository corticotropin injection, *SLE* systemic lupus erythematosus, *SLEDAI-2 K* SLE Disease Activity Index-2000, *SRI-4* SLE Responder Index-4, *TJC* total joint count, *tsDMARD* targeted synthetic disease-modifying antirheumatic drug, *VAS* visual analog scale

[a]LupusQOL includes eight domains (body image, burden to others, emotional health, fatigue, intimate relationships, pain, physical health, planning); here we report data only for the pain and fatigue domains

Table 2 Studies with pain and/or fatigue outcomes following RCI treatment in patients with symptomatic sarcoidosis

Study	Objective, design, and treatment	Outcomes and sample size	Key inclusion/exclusion criteria	Patient baseline characteristics	Fatigue outcomes	Pain outcomes
Baughman et al., 2017 [15]	*Objective:* To compare 2 doses of RCI in patients with advanced pulmonary sarcoidosis receiving prednisone *Design:* Prospective randomized study *Treatment:* RCI 80 U SC once a day for 10 days; 14 days after starting study (4 days after last scheduled dose), patients randomized 1:1 to 40 or 80 U RCI twice per week for 22 more weeks	*Primary endpoint:* Prednisone-sparing effect of RCI 40 IU vs 80 IU at week 7 (assessed modification of prednisone dose based on algorithm established by Baughman et al., 2002 [35]) *Fatigue and/or pain outcome(s)*: KSQ; SGRQ; FAS; steroid toxicity questionnaire *No. of patients:* Enrolled (N = 18); randomized to RCI 40 U (n = 9) and randomized to RCI 80 U (n = 8)	*Inclusion:* Diagnosis of pulmonary sarcoidosis based on standard ATS/ERS/WASOG criteria [36]; stable dose ≥ 5 mg prednisone for ≥ 3 months; deterioration of pulmonary disease in previous year *Exclusion:* Received anti-TNF antibody (e.g., infliximab, adalimumab) in prior 6 months; or receiving treatment for sarcoidosis-associated pulmonary hypertension	Median age, years (range): 40 U group, 58 (49–68); 80 U group, 59 (35–60) Gender (all patients): female (56%); male (44%) Use of prednisone: 100%	Median FAS (range): week 0, 28 (15–46); week 7, 26 (10–27); week 24, 22 (11–42); week 0 vs week 24, P = 0.0067	None

Table 2 continued

Study	Objective, design, and treatment	Outcomes and sample size	Key inclusion/exclusion criteria	Patient baseline characteristics	Fatigue outcomes	Pain outcomes
Chopra et al., 2019 [27]	*Objective:* To describe patient demographic and clinical characteristics, RCI utilization patterns and concomitant therapies, physicians' assessments of RCI effects on patients' health status *Design:* Retrospective chart review *Treatment:* RCI real-world use: Mean ± SD duration of RCI treatment 32.5 ± 35.6 weeks; 62% of patients continued RCI for ≥ 6 months	*Primary endpoint:* No predefined primary endpoint/outcome *Fatigue and/or pain outcome(s)*: Physicians' assessments of change in patients' health status after RCI therapy *No. of patients:* $N = 302$	*Inclusion:* Age ≥ 18 years; diagnosis of symptomatic sarcoidosis; treatment with RCI in previous 36 months; completely accessible medical record; completed individualized RCI course (based on disease severity and initial response) or received RCI ≥ 6 months at time of data collection *Exclusion:* Absence of symptoms	Mean ± SD age 51 ± 12 years Gender: women (52%); men (48%) Medications in prior 3 months (before starting RCI) for symptomatic sarcoidosis: oral corticosteroids (61%); biologics (24%); antimalarial agents (22%) Present before RCI initiation: fatigue (42%)	Physicians' assessments of change in patients' health post RCI Patient current status: Improved (95%); not improved (5%) Type of treatment response that improved due to RCI treatment: fatigue (29%)	None

ATS American Thoracic Society, *ERS* European Respiratory Society, *FAS* fatigue assessment scale, *GHS* general health status, *KSQ* King's sarcoidosis questionnaire, *QOL* quality of life, *RCI* repository corticotropin injection, *SC* subcutaneously, *SGRQ* Saint George's respiratory questionnaire, *TNF* tumor necrosis factor, *VAS* visual analog scale, *WASOG* World Association of Sarcoidosis and other Granulomatous Disorders

Table 3 Studies with pain and/or fatigue outcomes following RCI treatment in patients with noninfectious keratitis and uveitis

Study	Objective, design, and treatment	Outcomes and sample size	Key inclusion/exclusion criteria	Patient baseline characteristics	Fatigue outcomes	Pain outcomes
Uveitis						
Nelson et al., 2019 [22]	*Objective:* To describe patient demographic and clinical characteristics, utilization patterns of RCI and concomitant therapies, and physicians' assessments of patients' therapeutic response *Design:* Retrospective chart review *Treatment:* RCI real-world use Variable dosing and course of treatment 77% of patients prescribed initial regimen of RCI 40–80 U once or twice weekly	*Primary endpoint:* No predefined primary endpoint/outcome *Fatigue and/or pain outcome(s):* Physicians' impressions of therapeutic response (2 questions: What is the patient's current status? Please select outcomes that have improved as a result of RCI treatment) *No. of patients:* $N = 91$	*Inclusion:* Diagnosis of uveitis; received RCI in past 12 mo; completed course of RCI or receiving RCI at time of collection; complete medical records available *Exclusion:* Infectious eye inflammation; ophthalmic neoplasm; recent ophthalmic or orbital surgery (within 60 before diagnosis); recent eye trauma (within 60 days before diagnosis)	Mean ± SD age 41 ± 14 years Gender: female (62%); male (38%) Uveitis symptoms, % patients: Blurred vision (89%); light sensitivity (45%); floaters (44%); visual loss/acuity (44%); eye pain (37%); eye redness (33%)	None	Physicians' impressions of therapeutic response after RCI injection (% patients): Patient's current status: Improved (84%); same (15%); worsened (0) Outcomes that had improved as a result of RCI treatment: Improvements in pain (27%)
Noninfectious keratitis						
Wirta et al., 2021 [16]	*Objective:* To evaluate the efficacy and safety of RCI for the treatment of refractory severe noninfectious keratitis that had not adequately responded to treatment with standard-of-care therapies *Design:* Prospective open-label phase 4 trial *Treatment:* RCI 80 U SC twice weekly for 12 weeks, then tapering for 4 weeks (RCI reduced to 40 U twice weekly for 2 weeks, then 40 U once weekly for 2 weeks)	*Primary endpoint:* Proportion of patients with ≥ 12-point improvement in symptom bother domain of IDEEL questionnaire at week 12 and proportion of patients with ≥ 20%, 30%, and 50% improvement in symptom bother domain of IDEEL questionnaire at week 12 *Fatigue and/or pain outcome(s):* Patient-reported VAS pain item; burning and stinging items of the 4-symptom questionnaire *No. of patients:* $N = 35$	*Inclusion:* Age ≥ 18 years; normal lid anatomy; history of severe keratitis in 1 or both eyes and history of previous treatment for keratitis within previous 6 months; no symptomatic improvement or did not tolerate previous treatment with topical cyclosporine or lifitegrast; in ≥ 1 eye at screening and baseline have all of the following: inferior corneal fluorescein staining score ≥ 2 in any field, corneal sum fluorescein staining score ≥ 4, conjunctival sum lissamine green staining score ≥ 2, conjunctival redness score ± 1, Schirmer score ≥ 1 mm/5 min and ≤ 10 mm/5 min, and ODS ≥ 2 *Exclusion:* Any ocular condition that, according to investigator's opinion, could affect study parameters; history of LASIK or other ocular surgical procedure within 12 months of baseline visit; ocular trauma, penetrating intraocular surgery, refractive surgery, corneal transplantation, or eyelid surgery within 12 weeks before screening visit; any scheduled ocular surgical procedure during study; active or history of ocular herpes or other ocular infection within 30 days of prior baseline visit; have current punctal plugs, punctal occlusion, or history of nasolacrimal duct obstruction; unwillingness to avoid wearing contacts for 7 days before screening visit and for duration of study	Mean ± SD age 63 ± 10 years Sex: female (71%); male (29%) Keratitis in both eyes, % patients: 100%	None	Proportion of patients with complete resolution of ODS at week 12: 20.0% (95% CI 6.7–33.3%) Proportion of patients with complete resolution of each symptom in 4-symptom questionnaire at week 12: dryness 8.6% (95% CI 0–17.8%); grittiness 45.7% (95% CI 29.2–62.2%); burning 42.9% (95% CI 26.5–59.3%); stinging 62.9% (95% CI 46.8–78.9%) Mean change ± SD (95% CI) from baseline by VAS at week 12: pain 15.0 ± 20.2 (−23.1 to −6.9); eye dryness −22.2 ± 25.6 (−32.6 to −11.8); burning/stinging −13.5 ± 24.3 (−23.3 to −3.7); itching −10.1 ± 27.3 (−21.1 to 0.9); foreign body sensation −17.7 ± 22.5 (−26.7 to −8.6); eye discomfort −23.9 ± 25.4 (−34.2 to −13.7); photophobia −19.5 ± 26.5 (−30.2 to −8.8)

IDEEL impact of dry eye on everyday life, *LASIK* laser-assisted in situ keratomileusis, *ODS* ocular discomfort score, *RCI* repository corticotropin injection, *SC* subcutaneously, *VAS* visual analog scale

PROs such as pain VAS. The analyzed patients (mean age 60.1 years) were predominantly women (81%) and had a mean ± SD CDAI score of 29.7 ± 16.4, above the > 22 threshold for high disease activity [28, 29]. Most of these patients had been treated with a DMARD (96%) and glucocorticoids (92%). The 46% of patients with at least two RCI prescriptions had a mean ± SD of 152 ± 117 days lapsing from the start of RCI to the last RCI prescription. Compared with before starting RCI, the patients' mean ± SD pain VAS severity score significantly decreased (mean decrease − 1.1 ± 2.8; $P = 0.0056$) after starting RCI.

Fiechtner and Montroy [12] assessed FACIT-F at baseline and after RCI treatment initiation in a prospective open-label clinical trial of RCI in 10 adults with chronic moderately-to-severely active SLE flares despite standard treatment. The patients (median age 49 years) were all women, with a mean baseline SLEDAI-2 K score of 10. RCI treatment consisted of 80 U daily for 10 days, followed by an optional 5-day rescue period for patients experiencing partial or no response. These investigators reported statistically significant improvements in mean FACIT-F scores at day 14 and day 28 (both $P < 0.01$) after the start of RCI treatment compared with baseline.

One study included PRO data for both pain and fatigue [14, 25]. As part of a 24-week randomized, double-blind, clinical trial comparing RCI with placebo in 169 adults with persistently active SLE despite use of moderate-dose glucocorticoids, Askanase et al. [14, 25] reported findings at baseline and weeks 8, 16, and 24 using the LupusQOL PRO instrument, which measures fatigue, pain, and six other domains (body image, burden to others, emotional health, intimate relationships, physical health, and planning). The enrolled patients (median age 39.7 years) were predominantly women and had a mean SLEDAI-2 K score of 9.9. Patients were randomized to receive RCI 80 U or placebo every other day through week 4, then twice per week for 20 more weeks, for a total of 24 weeks. Patients in the RCI group had greater improvement compared with the placebo group in mean ± SD change from baseline for the LupusQOL pain domain at week 16 (mean, 20.6 ± 23.8 vs 12.4 ± 24.1; $P < 0.05$) and no statistically significant differences in the fatigue domain at weeks 8, 16, and 24. Exploratory post hoc subgroup analyses found greater improvements from baseline for RCI compared with placebo in LupusQOL pain and fatigue domains among patients who had higher disease activity as indicated by SLEDAI-2 K ≥ 10, CLASI-Activity ≥ 11, and/or BICLA. These improvements were above thresholds considered to indicate minimal clinically important difference (MCID) in patients with SLE [34].

Impact of RCI on Pain and Fatigue in Sarcoidosis

Two studies used PROs and/or physician-reported pain or fatigue measures in patients with sarcoidosis (Table 2) [15, 27]. In a prospective randomized study comparing two doses of RCI in 18 patients with pulmonary sarcoidosis, Baughman et al. [15] included PRO data from FAS at baseline and weeks 7 and 24 after initiation of RCI treatment. The patients had a median age of 59 years; most were women (56%), and all were using prednisone to treat sarcoidosis. All the patients were treated with RCI 80 U once a day for 10 days and, 4 days after the last scheduled dose, they were randomized 1:1 to continue treatment with RCI 40 or 80 U twice a week for 22 more weeks. The investigators reported data on the total patient population because they did not find statistically significant differences between the two RCI dosing groups. The median FAS significantly improved ($P = 0.0067$) from baseline (median 28, range 15–46) to 24 weeks after the start of RCI treatment (median 22, range 11–42).

A retrospective chart review by Chopra et al. [27] of data from 302 adults with sarcoidosis treated with RCI during the previous 36 months reported physicians' assessments of patients' response status by outcome domain (i.e., improved or not improved at the end of RCI therapy or of the prior 6 months if RCI was ongoing) and by type of treatment outcome (selecting from nine options, including fatigue) that had improved with RCI treatment. Patients had a mean ± SD age of 51 ± 12 years, 52%

were women, and 42% presented with fatigue before initiating RCI therapy. Most patients (61%) had been treated with oral corticosteroids for symptomatic sarcoidosis during the 3 months before initiating RCI therapy. The study did not report information on RCI dosing; the mean ± SD duration of RCI treatment was 32 ± 36 weeks, and 62% of patients continued to take RCI for at least 6 months. According to physicians' assessments, 29% of patients experienced improvement in fatigue after initiating RCI treatment.

Impact of RCI on Pain and Fatigue in Uveitis and Keratitis

Two studies included findings on PRO and/or physician-reported pain or fatigue measures in patients with uveitis or noninfectious keratitis (Table 3) [16, 22]. In a retrospective chart review of 91 patients with uveitis treated in the previous 12 months, Nelson et al. [22] reported data on physicians' assessments of patient's current status after RCI injection and type of observed improvements, including improvements in pain. Patients in this study had a mean ± SD age of 41 ± 14 years and were predominantly women (62%). The most common uveitis symptoms reported in these patients were blurred vision (89%), light sensitivity (45%), floaters (44%), visual loss/acuity (44%), and eye pain (37%). Most patients (77%) had been prescribed an RCI initial regimen of 40 to 80 U once or twice weekly. The dosing and course of treatment varied. After RCI injection, physicians' assessments noted improvements in 84% of patients' current status, primarily because of improvements in vision (86%) and improvements in pain (27%).

In a prospective open-label phase 4 trial in adults with severe noninfectious keratitis, Wirta et al. [16] reported data on PROs such as ODS, the four-symptom questionnaire (which included assessments of burning and stinging), and eye-specific VAS measures (which also included assessment of burning/stinging and pain). The enrolled patients (mean age 63 years) were predominantly women (71%), and all had keratitis in both eyes. Patients received RCI 80 U twice weekly for 12 weeks followed by a tapering sequence of 2 weeks of 40 U twice weekly and 2 weeks of 40 U once weekly. At week 12, 20% of patients had experienced complete resolution of ODS. According to the four-symptom questionnaire at week 12, 43% of patients had complete resolution of burning and 63% of stinging. The mean ± SD change from baseline by VAS at week 12 was − 13.5 ± 24.3 (95% CI − 23.3 to − 3.7) for burning/stinging and − 15.0 ± 20.2 (95% CI − 23.1 to − 6.9) for pain.

DISCUSSION

Across the different types of studies assessed (i.e., clinical trials, chart reviews, EMR real-world evidence) in this narrative review, the results were consistent with respect to the impact of RCI treatment on reducing pain and fatigue, regardless of whether the studies were open-label or randomized and blinded, analogous to the results obtained with other efficacy outcome measures.

In the four RA or SLE studies, patients were predominantly women (81–100%) with high disease activity despite ongoing treatment with DMARDs and other drugs [11, 12, 14, 23, 26]. In all four studies, either pain or fatigue was reduced and in two of the studies, both pain and FACIT-F were improved in responders or those with high disease activity. At the end of 12 weeks of open-label RCI treatment in a randomized withdrawal study in patients with active RA, the statistically significant decreases in mean FACIT-F scores and PGAP paralleled the finding that 62.9% of patients achieved the primary endpoint of DAS28-ESR < 3.2 and 65.3% achieved CDAI LDA (i.e., CDAI ≤ 10) [11, 31, 37]. An EMR analysis of data from 114 patients noted that, after the RCI index date, the significant decrease in pain VAS severity aligned with a clinically meaningful reduction in CDAI mean scores (− 9.7 ± 16.9, $P = 0.0101$), changing high RA activity to moderate RA activity, and with significant decreases in swollen (− 1.1 ± 2.8; $P = 0.0116$) and tender joint mean counts (− 3.3 ± 8.0; $P = 0.0128$) [23]. A small single-group clinical

trial reported significant improvements in mean FACIT-F scores from baseline to days 14 and 28 following RCI treatment initiation [12] in addition to significant improvements in the primary endpoint of mean SLEDAI-2 K, which decreased from 9.6 at baseline to 6.2 at day 14 and 4.0 at day 28 after RCI initiation (both comparisons $P < 0.01$).

In the two studies assessing pain and/or fatigue after treatment with RCI in adults with symptomatic sarcoidosis, the combined analysis of a randomized study of two doses of RCI reported significant improvements in median FAS from baseline to 24 weeks after RCI initiation ($P = 0.0067$) along with significant decreases in prednisone dosage ($P = 0.0078$) and other clinical efficacy measures, such as median standard uptake value of highest lung lesion [15]. A large retrospective chart review reported that by physicians' assessments of change in patients' health post-RCI treatment, 95% of patients with symptomatic sarcoidosis had improved because of treatment responses in overall symptoms (73%); lung function (38%); inflammation (33%); corticosteroid use, reduction, or discontinuation (32%); QOL (32%); and fatigue (29%) [28].

A retrospective chart review of patients with uveitis reported that physicians' assessments of patients' current health status showed improvements in 84% of patients, as marked by improvements in vision (86%), improvements in pain (27%), and improvements in vitreous haze (26%) [22], which translated to reductions in use of concomitant medications such as steroid eye drops, oral steroids, and intraocular steroids [22]. A prospective single-arm clinical trial in patients with severe keratitis reported meaningful mean changes from baseline to week 12 of RCI treatment for the VAS burning/stinging and pain measures and 50% of patients in the study met the primary endpoint of clinically important improvements (i.e., at least 12 points) in the symptom bother domain of the IDEEL questionnaire [16, 38].

CONCLUSIONS

As summarized in this review, data from patient- and physician-reported outcome measures in eight published studies suggest that, in addition to improving more traditional efficacy measures, RCI may also improve pain and fatigue outcomes in patients with RA, SLE, symptomatic sarcoidosis, uveitis, and noninfectious keratitis. To evaluate treatment effectiveness in future studies in these populations, pain and fatigue measures should be considered for inclusion alongside conventional efficacy assessments.

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