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REVIEW

Clinical and Economic Evaluation of Repository Corticotropin Injection: A Narrative Literature Review of Treatment Efficacy and Healthcare Resource Utilization for Seven Key Indications

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ABSTRACT

Introduction: Repository corticotropin injection (RCI; H.P. Acthar® Gel; Mallinckrodt Pharmaceuticals Inc., Hampton, NJ) is a highly purified, prolonged-release porcine preparation of adrenocorticotropic hormone (ACTH) analogue that is FDA-approved for treatment of 19 autoimmune and inflammatory disorders. The diverse physiological actions of RCI at the melanocortin receptors (MCRs) affect processes involved in inflammation, pigmentation, steroidogenesis, and immunomodulation. Although RCI has been approved to treat inflammatory and autoimmune diseases for more than 60 years, recent progress in understanding both MCRs and the effects of RCI in modulating immune responses has led to increased interest in RCI as a therapeutic choice. The objective of this narrative literature review is to summarize key clinical and economic data on RCI treatment of seven disorders: infantile spasms (IS), multiple sclerosis (MS) relapses, proteinuria in nephrotic syndrome, rheumatoid arthritis (RA), dermatomyositis/polymyositis (DM/PM), systemic lupus erythematosus (SLE), and symptomatic sarcoidosis based on published literature and product information. An extended report is available as the Academy of Managed Care Pharmacy (AMCP) Formulary dossier for H.P. Acthar® Gel.

Methods: Key studies of clinical efficacy and healthcare utilization and cost from 1956 to 2016 are summarized.

Results: The evidence supports the efficacy of RCI across the seven indications. RCI is effective as a first-line therapy for IS. For the other six conditions, RCI may improve clinical outcomes during exacerbations or when the condition is resistant to conventional treatments. Use of RCI is associated with reduced use of biologics, corticosteroids, and disease-modifying antirheumatic drugs. Initiation of RCI therapy in patients with IS, MS, RA, SLE, or DM/PM has been associated with lower post-therapy healthcare utilization and medical costs, including decreases in hospitalizations, hospital length of stay, outpatient visits, and emergency department visits.

Conclusion: The evidence suggests that RCI may improve inflammatory and autoimmune disease control and patient quality of life, particularly in complex patients, and yield

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INTRODUCTION

Autoimmune diseases have wide-ranging effects in the body, including neurologic, renal, musculoskeletal, dermatologic, and pulmonary effects, and can lead to dysfunction of multiple organs and tissues. These autoimmune diseases can be associated with substantial patient morbidity, disability, and impaired quality of life and they may impose significant long-term humanistic and economic burdens on families, healthcare systems, and society.

Autoimmune diseases are treated with a variety of therapeutic agents, including corticosteroids, immunosuppressants, immunomodulators, disease-modifying antirheumatic drugs (DMARDs), biologics, and nonsteroidal anti-inflammatory agents. Repository corticotropin injection (RCI; H.P. Acthar® Gel; Mallinckrodt Pharmaceuticals Inc., Hampton, NJ, USA) is a highly purified, prolonged-release preparation of adrenocorticotropic hormone (ACTH) in a 16% gelatin formulation that is administered via intramuscular or subcutaneous injection. It has been in clinical use for more than 60 years. RCI was first approved by the US Food and Drug Administration (FDA) in 1952, before the 1962 enactment of the Kefauver-Harris Amendment to the Federal Food, Drug and Cosmetic Act, an amendment that requires drug manufacturers to provide proof of effectiveness and safety before approval. For this reason, much of the available research on RCI consists of case series, uncontrolled or small randomized clinical trials, and retrospective analyses. Under the FDA's Drug Efficacy Study Implementation (DESI) program that was initiated following the Kefauver-Harris Amendment, RCI has been reviewed three times (in 1977, 1979, and 2010). With the most recent label update in 2015, RCI is currently approved for 19 indications (Table S1) (supplementary table is available online) [1]. RCI is the only naturally sourced form of ACTH approved for use in the USA.

RCI binds to melanocortin receptors (MCRs) and may have a diverse range of actions, including effects on inflammation, pigmentation, steroidogenesis, and immunomodulation [1, 2]. Current understanding of the melanocortin system points to a set of signaling pathways that play a role in inflammation control and immunomodulation [3]. In recent years, progress in understanding both MCRs and the effects of RCI in modulating immune responses has led to a renewed interest in RCI as a therapeutic choice [2].

The objective of this narrative literature review is to summarize the key clinical and economic data contained in the Academy of Managed Care Pharmacy (AMCP) Formulary dossier for H.P. Acthar® Gel for seven key indications: infantile spasms (IS), multiple sclerosis (MS) relapses, proteinuria in nephrotic syndrome, rheumatoid arthritis (RA), dermatomyositis/polymyositis (DM/PM), systemic lupus erythematosus (SLE), and symptomatic sarcoidosis [1, 4].

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CLINICAL VALUE OF REPOSITORY CORTICOTROPIN INJECTION

A number of studies in different therapeutic areas have assessed the clinical efficacy of RCI before and after treatment or compared RCI with placebo or other common therapies. These are described below and summarized in Table 1.

Infantile Spasms

IS, also known as West syndrome, refers to a unique epilepsy syndrome of early infancy (<2 years of age) in which patients present with a distinct seizure type [5–7]. Untreated IS is

Table 1 Clinical and healthcare utilization studies of adrenocorticotropic hormone and repository corticotropin injection

Citations	Objective, design, and endpoints	Key inclusion/exclusion criteria	Results
Clinical studies			
Infantile spasms			
Baram et al. [12]	Objective: To compare the efficacy of 2-week courses of high-dose ACTH vs. prednisone for IS treatment Study design: Randomized, single-blind trial Treatment groups: ACTH for 2 weeks (150 U/m^2/day in 2 divided doses) or oral prednisone (2 mg/kg/day in 2 divided doses) Sample size: 29 Outcomes: Resolution of clinical signs and symptoms	Inclusion criteria: Infants with clinical IS Exclusion criteria: Previous steroid or ACTH treatment	Results favored ACTH; 86.6% of infants treated with ACTH and 28.6% of infants treated with prednisone had cessation of spasms and resolution of hypsarrhythmia ($p = 0.002$)
Knupp et al. [13]	Objective: To evaluate early and sustained response to initial treatment of IS Study design: Prospective, observational, multisite study Treatment groups: ACTH, prednisolone, vigabatrin, and other (nonstandard) therapy (various dosing regimens) Sample size: 230 Outcomes: IS response rate; resolution of hypsarrhythmia on EEG at 2 weeks and 3 months	Inclusion criteria: Children with new onset IS between 2 months and 2 years of age Exclusion criteria: Early infantile epileptic encephalopathy; missing treatment, response, or follow-up data	At 2 weeks, 68% (66/97) of those who were receiving ACTH and 56% (30/54) of those who were receiving prednisolone had responded ($p = 0.13$); the ACTH response rate was significantly higher than in those receiving vigabatrin (49%, 23/47; $p = 0.027$) or nonstandard treatment (22%, 7/32; $p < 0.001$). At 3 months, 55% (53/97) of infants receiving ACTH had responded, compared with 39% (21/54) for prednisolone, 36% (17/47) for vigabatrin, and 9% (3/32) for other therapies (overall $p < 0.001$). The response rate in the ACTH group was significantly higher than in the vigabatrin group ($p = 0.038$) and marginally higher than in the prednisolone group ($p = 0.06$). Of children who received high-dose ACTH, 58% (46/80) responded, compared with 38% (6/16) of those who received low/intermediate-dose ACTH
Multiple sclerosis relapse			
Rose et al. [20]	Objective: To investigate ACTH gel in the treatment of patients with acute MS relapses Study design: Randomized, double-blind, placebo-controlled, multisite trial Treatment groups: 40 U RCI or placebo gel IM twice daily for 7 days, 20 U twice daily for 4 days, and 20 U daily for 3 days Sample size: 197 patients Outcomes: Disability Status Scale administered weekly for 4 weeks	Inclusion criteria: Neurologic signs of disseminated CNS disease with clearly defined period of worsening (bout) within previous 8 weeks Exclusion criteria: Advanced CNS disease or complicating disease processes in their first bout, recent steroid or RCI therapy	Improvement in Disability Status Scale was seen in 65% of ACTH gel patients compared with 48% of patients in the placebo group ($n = 94$); between-group differences were significant at weeks 2 and 4. There was a 43% greater responder rate at week 1 with ACTH relative to placebo (70% vs. 49%; $p < 0.01$) and a 30% greater responder rate at week 3 (86% vs. 66%; $p < 0.01$). The average number of improved standard neurological examination items was greater for ACTH than placebo for each of the 4 weekly intervals (all $p < 0.01$)
Proteinuria in nephrotic syndrome			
Bomback et al. [27]	Objective: To collect prospective study data on ACTH treatment in resistant glomerular disease Study design: Prospective, nonblinded, open-label trial Treatment: ACTH gel (40 U SC twice weekly for 2 weeks, then 80 U twice weekly SC for 22 weeks) Sample size: 15 (5 with resistant MN, 5 with MCD or FSGS, and 5 with resistant IgA nephropathy) Outcomes: Proteinuria full or partial remission	Inclusion criteria: MN or MCD/FSGS with at least 2 previous immunosuppressive therapies or IgA nephropathy and receiving maximally tolerated renin–angiotensin–aldosterone system blockage Exclusion criteria: Age 18 years or younger, estimated glomerular filtration rate <30 mL/min/1.73 m^2, use of a monoclonal antibody within previous 6 months, or cyclophosphamide within previous 3 months, and others	Proteinuria was reduced in 8 of 15 patients. Two MN, 1 MCD, and 1 FSGS patient achieved partial remission. Two patients achieved complete remission

Table 1 continued

Citations	Objective, design, and endpoints	Key inclusion/exclusion criteria	Results
Bomback et al. [28]	Objective: To evaluate the initial use of RCI in patients with refractory nephrotic syndrome Study design: Retrospective case series Treatment: RCI Sample size: 21 Outcomes: Complete remission, partial remission, limited response, or no response	Inclusion criteria: Diagnosis of idiopathic nondiabetic nephrotic syndrome treated with RCI; at least 6 months of full data available Exclusion criteria: N/A	Of 21 patients who completed RCI treatment, 7 achieved partial remission and 4 achieved complete remission. Of 11 patients with idiopathic MN, 3 achieved complete remission and 6 achieved partial remission despite having previously failed a mean of 2.4 therapies. Of 10 patients with nephrotic syndrome of other etiologies, 1 with IgA nephropathy achieved complete remission, 1 with FSGS achieved partial remission, and 1 with MPGN had a limited response to therapy
Hogan et al. [29]	Objective: To assess the use of ACTH in patients with proteinuria due to FSGS previously treated with other therapies Study design: Nonrandomized, two-site trial Treatment groups: (1) 40 U SC weekly for 2 weeks, 80 U SC twice weekly for 2 weeks, then 80 U SC twice weekly for 10 weeks ($n = 12$) or (2) 40 U SC twice weekly for 2 weeks, then 80 U SC twice weekly for a target duration of 24 weeks ($n = 7$) or (3) heterogeneous treatment regimens ($n = 5$) Sample size: 24 Outcomes: Complete remission of proteinuria	Inclusion criteria: Proteinuria due to biopsy-proven FSGS and evidence of nephrotic syndrome Exclusion criteria: Being of childbearing age and not using birth control, recent active immune therapy, pregnancy, decreased renal function, known contraindications to RCI therapy	Seven patients achieved remission (2 complete and 5 partial responses). Five patients had a sustained remission and 2 experienced proteinuria relapse (median follow-up of 90 weeks)
Hladunewich et al. [30]	Objective: To assess the safety and efficacy of RCI in adults with biopsy-proven idiopathic MN and proteinuria due to nephrotic syndrome Study design: Randomized, nonblinded, dose-finding phase 1b/2 pilot study Treatment groups: 40 U or 80 U RCI once or twice a week for 12 weeks (1 dose per week for 4 weeks, then 2 doses per week) Sample size: 20 Primary outcomes: Changes in measures of nephrotic syndrome (improvements in proteinuria, serum albumin, and cholesterol profile), documented side effects, and toxicity Secondary outcomes: Complete remission (proteinuria <0.3 g/day), partial remission (reduction in proteinuria by >50% with a final urine protein <3.5 and >0.3 g/day), and no response (reduction in proteinuria by <50% or worsening of proteinuria)	Inclusion criteria: Biopsy-proven idiopathic MN, age >18 years Exclusion criteria: Documented resistance to immunosuppressive routines used in idiopathic MN; recent use of glucocorticoids, calcineurin inhibitors, mycophenolic mofetil or alkylating agents; active infection; secondary cause of membranous nephropathy, diabetes mellitus; acute thrombosis requiring anticoagulation therapy; pregnant or nursing	A >50% decrease in proteinuria was noted in 50% of patients at completion of treatment and in 65% of patients at 12 months. Proteinuria decreased from a mean (± SD) of 9.1 ± 3.4 g/day at baseline to 6.2 ± 4.8 g/day at treatment completion and 3.9 ± 4.2 g/day at 12 months ($p < 0.001$), with significant improvements in serum albumin and total and LDL cholesterol (all $p < 0.001$). Of 4 patients receiving 40 U RCI, 1 (25%) achieved partial remission. Of 16 patients receiving 80 U RCI, 2 (12.5%) achieved partial remission and 9 (56.3%) achieved full remission
Madan et al. [31]	Objective: To examine the efficacy and safety of RCI treatment in patients with nephrotic syndrome Study design: Retrospective multicenter case series Treatment: RCI Sample size: 44 Outcomes: Type of nephrotic syndrome, response to treatment	Inclusion criteria: Biopsy-confirmed nephrotic syndrome, 24-h proteinuria level or urine protein: creatinine ratio before and after ≥6 months of RCI treatment Exclusion criteria: N/A	Thirty-seven patients completed treatment. A proteinuria reduction ≥30% occurred in 81.1% (30/37) of patients. A proteinuria reduction ≥50% occurred in 62.2% (23/37). Mean reduction in proteinuria post-treatment was 3984.8 ± 4069.1 mg/day ($p < 0.0001$). Total cholesterol declined and serum albumin increased. Remission of proteinuria occurred in 56.8% (21/37) of patients, either partial (17/37, 45.9%) or complete (4/37, 10.8%)

Table 1 continued

Citations	Objective, design, and endpoints	Key inclusion/exclusion criteria	Results
Rheumatoid arthritis			
Gaylis et al. [34]	Objective: To assess effects of RCI on clinical and structural endpoints in patients with early RA Study design: Prospective, observational, open-label trial Treatment: MTX 15 mg weekly plus RCI 80 U weekly or biweekly for 24 weeks Sample size: 10 Outcomes: Clinical response, remission	Inclusion criteria: At least 6 tender and swollen joints; a CDAI score >6.0; and osteitis, synovitis, or erosions on MRI Exclusion criteria: N/A	Eight of 10 patients showed a clinical response as measured by improvement in CDAI score. Two patients achieved clinical remission, 3 had low disease activity, 3 had moderate disease activity, 1 had high disease activity, and 1 patient terminated treatment early because of lack of efficacy. All 5 patients who received biweekly doses demonstrated a clinical response and showed a structural response of regression of synovitis and regression or nominal change in osteitis
Gillis et al. [35]	Objective: To assess efficacy and safety of SC injections of RCI as adjunctive therapy in adults with active RA Study design: Prospective, nonrandomized, open-label, single-center trial Treatment: RCI 80 U SC every 72 h for 12 weeks Sample size: 6 Primary outcomes: Tender joint count, swollen joint count, change in 20-item Health Assessment Questionnaire Secondary outcomes: ESR level, CRP, and patient and physician global VAS, change in Disease Activity Score	Inclusion criteria: Active RA, not responding sufficiently to ≥2 biologic agents with different modes of action Exclusion criteria: N/A	At 12 weeks, all 6 patients had reduced tender and swollen joint counts. Three showed improvement in Health Assessment Questionnaire score and 6 showed improvement in Disease Activity Score. Improvements were seen in ESR (4/6), CRP level (4/6), and patient (5/6) and physician (6/6) global VAS. Improvements in all measures generally receded 4 weeks after treatment ended
Dermatomyositis/polymyositis			
Levine [39]	Objective: To investigate efficacy and safety of ACTH in women with refractory DM or PM Study design: Retrospective observational case series Treatment: RCI 80 U SC once weekly or twice weekly for 12 weeks as short-term adjunctive treatment Sample size: 5 Outcomes: Muscle strength, pain, and function	Inclusion criteria: Female; refractory DM or PM; disease exacerbation; no response to or inability to tolerate side effects of corticosteroids, IV immunoglobulin, or steroid-sparing drugs for at least 60 days Exclusion criteria: N/A	Muscle strength, pain, and function improved in all 5 patients. Three patients with impaired ambulation before treatment returned to independent ambulation, and 1 was able to return to work
Aggarwal et al. [40]	Objective: To evaluate the efficacy, safety, tolerability, and steroid-sparing effect of RCI in refractory adult DM/PM Study design: Prospective, uncontrolled, open-label trial Treatment: 80 U RCI twice weekly for 6 months Sample size: 12 Outcomes: Improvement in myositis as defined by the International Myositis Assessment and Clinical Studies Group (IMACS); safety; tolerability; steroid-sparing effect; myositis response criteria	Inclusion criteria: N/A Exclusion criteria: N/A	10 of 11 patients (91%) completing the study experienced improvement in myositis at 2–3 months; sustained improvement occurred in 8 patients (73%). One patient stopped treatment because of heart block. Steroid dose decreased from a median (IQR) of 15 mg at baseline to 1.25 mg at last visit

Table 1 continued

Citations	Objective, design, and endpoints	Key inclusion/exclusion criteria	Results
Systemic lupus erythematosus			
Fiechtner and Montroy [44]	Objective: To assess the efficacy and safety of RCI in reducing the intensity of flares in patients with SLE Study design: Prospective open-label trial Treatment groups: RCI (80 U/mL by SC injection for 10 days, with an optional 5 additional days) Sample size: 10 Primary outcomes: Reduction in flare intensity based on SLEDAI-2 K scores Secondary outcomes: Physician Global Assessment; Patient Global Assessment; Lupus Quality of Life scale; Functional Assessment of Chronic Illness Therapy-Fatigue scale; British Isles Lupus Assessment Group Index scores; and markers of inflammation, including ESR and CRP	Inclusion criteria: Diagnosis of SLE with chronic disease activity requiring ongoing treatment or observation for ≥8 weeks, moderately to severely active disease, meet ACR criteria for SLE flare, receipt of prednisone ≤20 mg/day or equivalent for ≥4 weeks or immunosuppressive or antimalarial treatment for SLE for ≥8 weeks Exclusion criteria: Any new prednisone therapy or change in current oral prednisone therapy, receipt of ≥1 prescribed NSAID, or surgery within past 4 weeks; history of allergy or reaction to any component of RCI or live or attenuated vaccine; and others	At day 28 there were statistically significant reductions in SLEDAI-2 K scores and improvements in Physician Global Assessment, Patient Global Assessment, Functional Assessment of Chronic Illness Therapy-Fatigue, and erythrocyte sedimentation rate (all $p \leq 0.5$)
Furie et al. [45]	Objective: To evaluate the efficacy of RCI added to standard of care in patients requiring moderate-dose corticosteroids for symptomatic SLE Study design: Prospective, randomized, double-blind, placebo-controlled, phase 4 pilot study Sample size: 38 Treatment: RCI 40 U daily or 80 U every other day or volume-matched placebo gel for 4 weeks, then RCI tapered to twice weekly for 4 weeks Outcomes: Change in composite measure of hybrid SLEDAI (hSLEDAI), BILAG, and CLASI scores, and tender and swollen joint count	Inclusion criteria: Persistently active SLE and/or cutaneous involvement (hSLEDAI score >2), moderate to severe rash with arthritis and/or skin involvement and BILAG score of A or B in mucocutaneous and/or musculoskeletal systems despite a stable dose of prednisone for ≥4 weeks Exclusion criteria: Initiation of corticosteroid treatment within previous 2 months; active nephritis or active CNS lupus requiring treatment within previous 3 months, and other criteria	At week 8, the proportion of responders was higher in RCI groups (RCI 40 U, 53.8%; RCI 80 U, 33.3%), but difference from placebo (27.3%) was not statistically significant. Statistically significant improvements were seen in the RCI groups for hSLEDAI, BILAG, and CLASI scores
Symptomatic sarcoidosis			
Salomon et al. [51]	Objective: To record observations on effects of RCI and cortisone therapy in patients with systemic sarcoidosis of the lungs Study design: Case series Treatment: RCI 80 U IM each day, with a gradual taper, for a total dose of 1500–2000 U, or oral cortisone for 35–45 days (300 mg daily for 3 days, 200 mg daily for 5 days, and 100 mg daily for the remaining 34 days, for a total dose of 5300 mg) Sample size: 5 Outcomes: Lesions, lung volume, vital capacity, residual volume, ratio of residual volume to total lung capacity, dyspnea, cough, and general well-being	Inclusion criteria: Active confirmed systemic sarcoidosis of the lungs Exclusion criteria: N/A	RCI and cortisone markedly suppressed sarcoidosis lesions in all 5 patients. However, no patients experienced full remission

Table 1 continued

Citations	Objective, design, and endpoints	Key inclusion/exclusion criteria	Results
Baughman et al. [52]	Objective: To present experience with RCI to treat sarcoidosis Study design: Retrospective observational study Treatment: RCI Sample size: 47 Outcomes: Response to treatment, based on the response of the target organ, as improved disease, stable disease, or no response to treatment	Inclusion criteria: All patients with sarcoidosis treated with RCI at two centers and with at least 6 months of follow-up data Exclusion criteria: N/A	All patients were initially treated with RCI 80 IU (IM or SC) twice a week. Of 47 cases reviewed, 18 discontinued drug use within 6 months because of cost, death, drug toxicity, or noncompliance. Of the remaining 29 patients, 11 (38%) had objective improvement in one or more organs after ≥3 months of RCI treatment. Of 21 patients treated for ≥6 months, 11 had improvements in ≥1 organ and 10 had stable disease; 2 had a relapse. Of 19 patients receiving prednisone at baseline, 17 were able to reduce prednisone reduce by >50%
Healthcare resource utilization studies			
Infantile spasms			
Gold et al. [53]	Objective: To describe healthcare resource utilization and costs resulting from early (within 30 days of diagnosis) versus late (30 days after diagnosis) treatment with RCI to manage IS Study design: Retrospective observational study of healthcare claims data Treatment: RCI Sample size: 252 Outcomes: Adjusted 12-month mean number of outpatient and inpatient services, medications, and costs	Inclusion criteria: Age <2 years at time of IS diagnosis Exclusion criteria: Not continuously enrolled in health plan for ≥3 months before and ≥12 months after index date; subsequent diagnosis of tuberous sclerosis complex	Of 252 patients, 191 (76%) had early RCI treatment and 61 (24%) had late treatment. Early RCI treatment was associated with 3.8 fewer outpatient services (99% CI, −6.7 to −0.7)
Multiple sclerosis relapse			
Gold et al. [54]	Objective: To describe healthcare resource utilization and costs in patients with MS relapse treated with RCI vs. PMP or IVIG Study design: Retrospective observational study of healthcare claims data Treatment: RCI vs. PMP or IVIG Sample size: 439 (12-month analysis); 228 (24-month analysis) Outcomes: 12-month and 24-month mean number and cost of hospitalizations, outpatient services, and prescription medications	Inclusion criteria: Diagnosis of MS; ≥2 relapses with first relapse treated with IVMP and second relapse treated with RCI, PMP, or IVIG within 30 days of exacerbation Exclusion criteria: Not continuously enrolled in health plan for ≥6 months before and ≥12 months (for 12-month analysis) or ≥24 months (for 24-month analysis) after index date	In the 12-month adjusted analysis, compared with the PMP/IVIG group ($n = 226$), the RCI group ($n = 213$) had fewer hospitalizations (0.2 vs. 0.4; $p = 0.01$) and outpatient services (29 vs. 43; $p = 0.0001$), more prescription medications (36 vs. 30; $p = 0.0001$), lower inpatient costs (US$15,000 lower; $p = 0.001$) and lower outpatient costs (US$54,000 lower; $p = 0.0001$), and similar total costs. Results were similar for the 24-month analysis
Rheumatoid arthritis			
Wu et al. [55]	Objective: To describe healthcare resource utilization and costs for management of RA before and after treatment with RCI Study design: Retrospective observational study of healthcare claims data Treatment: RCI Sample size: 180 Outcomes: Healthcare utilization rates and costs for hospitalizations, ED visits, outpatient services, and drugs before and after initiation of treatment with RCI	Inclusion criteria: Age ≥18 years with RA Exclusion criteria: N/A	Healthcare utilization before vs. after treatment: Hospitalizations: All-cause, 42 vs. 25 per 1000 patient-years, $p < 0.01$; RA-related, 13 vs. 4 per 1000 patient-years, $p < 0.01$ ED visits: All-cause, 43 vs. 23 per 1000 patient-years, $p = 0.04$; RA-related, 8 vs. 1 per 1000 patient-years, $p < 0.01$ Outpatient services: All-cause, 56 vs. 47 per patient-year, $p < 0.01$; RA-related, 10 vs. 5 per patient-year, $p < 0.01$ Costs before vs. after treatment: Drugs: US$273 vs. US$4379 PPPM, $p < 0.01$ Medical: US$658 vs. US$93 PPPM, $p < 0.01$

Table 1 continued

Citations	Objective, design, and endpoints	Key inclusion/exclusion criteria	Results
Dermatomyositis/polymyositis			
Knight et al. [56]	Objective: To compare real-world healthcare resource utilization and costs in patients with DM/PM treated with RCI vs. IVIG and/or rituximab Study design: Retrospective observational study of commercial healthcare claims data; propensity score matching Treatment: RCI vs. IVIG and/or rituximab Sample size: 1134 Outcomes: Mean number and costs of hospitalizations and outpatient visits, mean hospital length of stay, mean medication costs, mean total nonmedical costs	Inclusion criteria: Diagnosis of DM/PM, treatment with RCI, IVIG and/or rituximab Exclusion criteria: N/A	Compared with IVIG, RCI had fewer hospitalizations (0.09 vs. 0.17 PPPM; $p = 0.049$), hospital outpatient department (HOPD) visits (0.60 vs. 1.39 PPPM; $p < 0.001$), and physician office visits (2.01 vs. 2.33 PPPM; $p = 0.035$) and shorter mean length of stay (3.24 days vs. 4.55 days; $p = 0.004$). Compared with rituximab, RCI had fewer HOPD visits (0.56 vs. 0.92; $p < 0.001$). Compared with IVIG + rituximab, RCI had shorter length of stay (2.18 days vs. 5.15; $p < 0.001$) and fewer HOPD visits (0.53 vs. 1.26; $p < 0.001$). Total mean nonmedication PPPM costs were lower for RCI compared with IVIG (US$2126 vs. US$3964; $p < 0.001$), rituximab (US$2008 vs. US$2607; $P = 0.018$), and IVIG + rituximab (US$1234 vs. US$4858; $p < 0.001$)
Systemic lupus erythematosus			
Wu et al. [57]	Objective: To describe the profile of patients with SLE initiating RCI treatment Study design: Retrospective observational study of healthcare claims data Treatment: RCI Sample size: 29 Outcomes: Hospitalization and outpatient visit rates and costs before and after RCI treatment	Inclusion criteria: Age ≥18 years with ≥2 diagnoses of SLE and RCI treatment	Compared with the preindex period, the postindex period had fewer hospitalizations PPPM (0.075 vs. 0.061) and ED visits (0.081 vs. 0.046) visits postindex compared with preindex. Total medical costs were lower postindex (US$5869 vs. US$3724) as were inpatient costs (US$3192 vs. US$799) and ED costs (US$163 vs. US$84). Total postindex costs were higher (US$6774 vs. US$11,167 PPPM), largely driven by higher pharmacy costs (US$905 vs. US$7443)
Multiple rheumatic conditions			
Myung et al. [58]	Objective: To describe the profile of patients with RA, DM/PM, or SLE initiating RCI treatment Study design: Retrospective observational study of healthcare claims data Treatment: RCI Sample size: 2749 Outcomes: Demographic characteristics, patterns of RCI, and concomitant medication use	Inclusion criteria: ≥1 claim with diagnosis code for RA, DM/PM, or SLE and any use of RCI Exclusion criteria: Claim for nonrheumatologic condition associated with RCI use (multiple sclerosis, proteinuria)	Most patients received 80 U of RCI twice weekly. The proportions of patients who used a corticosteroid were lower after RCI initiation than before (RA, 67% preindex and 54% postindex; SLE, 73% preindex and 58% postindex; DM/PM, 76% preindex and 58% postindex; all $p < 0.05$). In RA patients who had consistently taken corticosteroids for 24 weeks before RCI initiation, the postindex mean corticosteroid dose (11.47 ± 1.63 mg/day supply) was 28% lower than in the preindex period (15.86 ± 1.71 mg/day supply). The proportions of RA and SLE patients receiving biologics and of RA, SLE, and DM/PM patients receiving DMARDs were lower after RCI initiation (all $p < 0.05$)

ACR American College of Rheumatology, *ACTH* adrenocorticotropic hormone, *BILAG* British Isles Lupus Assessment Group, *CDAI* Clinical Disease Activity Index, *CLASI* Cutaneous Lupus Erythematosus Disease Area and Severity Index, *CNS* central nervous system, *CRP* C-reactive protein, *DMARD* disease-modifying antirheumatic drug, *DM/PM* dermatomyositis/polymyositis, *ED* emergency department, *ESR* erythrocyte sedimentation rate, *FSGS* focal segmental glomerulosclerosis, *IM* intramuscular, *IQR* interquartile range, *IS* infantile spasms, *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone, *MCD* minimal change disease, *MN* membranous nephropathy, *MPGN* membranoproliferative glomerulonephritis, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *MTX* methotrexate, *N/A* not available/not applicable, *NSAID* nonsteroidal antiinflammatory drug, *PMP* plasmapheresis, *PPPM* per patient per month, *RA* rheumatoid arthritis, *RCI* repository corticotropin injection, *SC* subcutaneous, *SLE* systemic lupus erythematosus, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *U* unit, *VAS* visual analogue scale

associated with developmental delay, autism, mental retardation, and an 11% mortality rate by age 2 years [5–8]. In a study of 244 infants aged 0–18 months, a delay in time to diagnosis following initial presentation was associated with cognitive abnormalities (median time to diagnosis, 18 vs. 6 days; $p < 0.001$) and motor abnormalities (median time to diagnosis, 17.5 vs. 6 days; $p < 0.001$) [9]. Outcomes may therefore be improved by early recognition of IS and immediate, effective treatment [6, 8, 10].

Compared with prednisone and conventional antiepileptic drugs, RCI may be more efficacious for the treatment of IS. RCI has orphan drug designation in the USA for treatment of IS [11]. In a US randomized controlled trial of 29 infants (median age, 6 months), 86.6% of infants treated with RCI (150 U/m^2/day) and 28.6% of infants treated with prednisone (2 mg/kg/day) ($p = 0.002$) had cessation of spasms and resolution of hypsarrhythmia after 2 weeks of therapy [12]. The most frequently reported adverse events in RCI-treated infants were irritability and voracious appetite.

More recently, a US study of 230 infants at 22 centers participating in the National Infantile Spasms Consortium reported that 55% of infants receiving RCI as initial treatment responded to therapy, compared with 39% for oral corticosteroids, 36% for vigabatrin, and 9% for other therapies ($p < 0.001$) [13].

The 2004 IS guideline of the American Academy of Neurology and Child Neurology Society recommends ACTH for short-term control of IS, supported by strong (level B) evidence [5]. Although the guideline refers to ACTH, RCI is the only form of ACTH approved for use in the USA, as noted previously. Based on three studies of RCI [14–16] and one study of synthetic ACTH [14–16], the 2012 guideline update recommends that low-dose ACTH be considered as an alternative to high-dose ACTH for treatment of IS (level B evidence) [6].

Multiple Sclerosis Relapses

MS is a complex and chronic demyelinating autoimmune neurological disorder. It is most frequently diagnosed between 20 and 40 years of age and is a leading cause of disability in this age group [17]. Acute relapses in MS may present with severe symptoms. To decrease inflammation and hasten recovery, a short course of corticosteroids (high-dose intravenous [IV] or oral) is often prescribed. However, if a patient does not respond or presents with breakthrough disease, ACTH, IV immunoglobulin (IVIG), or plasma exchange (plasmapheresis; PMP) may be required [18]. In the USA, RCI was first approved for treatment of MS exacerbations in 1978 and is currently indicated for treatment of acute exacerbations of MS in adults [1, 19]. Intravenous immunoglobulin and PMP are not FDA-approved therapies for relapses in MS.

The efficacy of RCI compared with placebo or other common therapies for the treatment of MS relapses has been evaluated. A large randomized, controlled, double-blind, multicenter trial found that RCI was superior to placebo for reducing the duration of relapse [20]. In a small study comparing routes of administration, intramuscular and subcutaneous administration of a 5-day course of RCI produced a comparable decrease in symptoms [21].

Both the National Multiple Sclerosis Society and the American Academy of Neurology have noted that alternative treatment options are needed for patients who experience MS relapse but do not respond to, cannot tolerate, or do not wish to take steroids [22, 23]. Thus, for patients needing an alternative treatment, RCI may provide an option.

Proteinuria in Nephrotic Syndrome

Nephrotic syndrome is a constellation of renal and extrarenal signs and symptoms that includes edema, proteinuria, hypoalbuminemia, lipiduria, hyperlipidemia, and hypercoagulability. It is caused by several systemic diseases and by primary insult to the kidney. Primary renal causes of nephrotic syndrome include minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, immunoglobulin A (IgA) nephropathy, and membranoproliferative glomerulonephritis,

and nephrotic syndrome may occur secondary to systemic diseases such as diabetes and systemic amyloidosis [24–26]. In patients with resistant glomerular disease, RCI is a treatment option, along with conventional therapy. It is indicated for inducing diuresis or remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type and in nephrotic syndrome due to lupus erythematosus [1].

Several studies have shown that RCI reduces proteinuria in several subtypes of treatment-resistant nephrotic syndrome: idiopathic membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease, membranoproliferative glomerulonephritis, lupus nephritis, and IgA nephropathy [27–31].

Rheumatoid Arthritis

RA is an autoimmune disease that leads to progressive destruction of the joints and associated cartilage [32]. It is associated with several comorbidities, including cardiovascular and pulmonary manifestations, skeletal disorders, cognitive effects, infection, and malignancies [33].

RCI is an FDA-approved adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) and for use in "selected cases who may require low-dose maintenance therapy" [1]. It has been shown to be effective in combination with methotrexate in terms of clinical response, inducing remission and slowing structural changes, with few serious adverse events observed [34, 35]. In an open-label study, 10 patients with early RA and at least six tender and swollen joints were treated with methotrexate plus RCI either weekly ($n = 5$) or biweekly ($n = 5$) [34]. An improved Clinical Disease Activity Index (CDAI) score was observed in eight patients. In the five patients who received RCI biweekly, both clinical and structural improvements were seen. A second open-label study of RA patients with an inadequate response to two or more biologic agents with different modes of action ($N = 6$) found that treatment with RCI for 12 weeks led to reductions in tender and swollen joint counts and improvements in Disease Activity Score for RA (DAS28), Patient Global Visual Analogue Scale (VAS), and Physician Global VAS in all patients [35].

Dermatomyositis and Polymyositis

DM and PM are autoimmune connective tissue diseases that are characterized by chronic inflammation of proximal skeletal muscles. DM also affects the skin and may affect the joints, esophagus, heart, and lungs. Patients with DM or PM typically present with slowly progressive weakness and reduced endurance in the muscles of the neck, shoulders, and pelvis [36–38].

Patients with DM or PM may experience clinical benefit from RCI therapy. In a case series study, five patients experiencing a disease exacerbation who had either failed or experienced adverse effects with conventional treatment were treated with RCI once or twice weekly for 12 weeks [39]. All patients showed improvement in manual muscle testing scores at 12 weeks, and no patients experienced significant adverse events. In an open-label uncontrolled study of RCI (80 U twice weekly for 6 months), 10 of 11 patients (91%) experienced improvement in myositis as defined by the International Myositis Assessment and Clinical Studies Group (IMACS) [40]. In addition, RCI was found to be generally safe, well tolerated, and steroid sparing.

Other than corticosteroids, RCI is the only FDA-approved drug for the treatment of DM/PM. It is indicated for use during an exacerbation or as maintenance therapy in selected cases [1].

Systemic Lupus Erythematosus

SLE is a systemic illness characterized by immune hyperactivity and the production of antinuclear, anticytoplasmic, and antiphospholipid antibodies. Patients typically present with fatigue, malaise, fever, arthralgia, myalgia, headache, loss of appetite, weight loss, and rash. The disease may progress to multiple end-organ involvement, resulting in photosensitivity, arthritis, and serositis as well as renal,

neurological, and other disorders [41–43]. During the course of the disease, intermittent acute relapses or flares may result in tissue damage. RCI is indicated during an exacerbation or as maintenance therapy in selected cases of SLE [1].

In a single-arm, uncontrolled, open-label study of 10 female patients with moderate-to-severe SLE who were receiving conventional therapy and experiencing a disease flare, adjunctive RCI treatment for 10 days, with an optional five additional days, led to reduction in disease activity and to improvement in functional status, quality of life, and erythrocyte sedimentation rate at 28 days [44]. No treatment-related serious or unexpected adverse events were observed. In an 8-week randomized controlled trial of RCI for the treatment of persistently active SLE, 38 participants received RCI 80 U every other day ($n = 13$), RCI 40 U daily ($n = 13$), or placebo ($n = 12$) [45]. Disease activity was reduced in the RCI groups compared with placebo, including statistically significant decreases in the Hybrid SLE Disease Activity Index and the British Isles Lupus Assessment Group index in both treatment groups at 8 weeks and in tender swollen joint count in the 80 U RCI group at 8 weeks.

Symptomatic Sarcoidosis

Sarcoidosis is a chronic inflammatory granulomatous disease that primarily affects the lungs (90% of affected patients have pulmonary involvement), although other organs such as the skin and eyes may be involved [46–48]. The disease follows a variable natural course, ranging from asymptomatic to a progressive disease that may be life threatening [48, 49]. Patients may be asymptomatic or have signs and symptoms such as cough, fever, weight loss, chest pain, painful ankle swelling, painful red nodules on the shins, eye pain, and blurred vision [50]. Treatment is generally reserved for symptomatic disease. RCI is an FDA-approved treatment for symptomatic sarcoidosis [1].

RCI was reported to be effective for symptomatic sarcoidosis as early as the 1950s. A case series study of patients receiving RCI ($n = 4$) or cortisone ($n = 1$) reported that treatment with RCI led to improvements in lung function and regression of skin, peripheral lymph node, parotid gland, and eye lesions [51]. In a recent retrospective chart review of patients with advanced sarcoidosis, 27 of 29 patients who received RCI (alone or in combination with steroids) for 6 months or longer experienced an improvement in their disease and 11 experienced objective improvement in the health of one or more affected organs. In addition, 17 of 19 patients receiving concomitant prednisone were able to reduce their prednisone dose by more than 50% [52]. Further evaluation of RCI therapy for symptomatic sarcoidosis is warranted, and prospective studies are underway.

HEALTHCARE UTILIZATION AND COSTS

Evidence in multiple therapeutic areas suggests that use of RCI decreases healthcare utilization, which may be associated with lower expenditures from a healthcare systems perspective. Key outcomes data are summarized in Table 1 and additional data are available in the AMCP dossier [4]. In some instances, these reductions in resource use may mitigate or potentially negate the increased medication costs through medical cost offsets.

Infantile Spasms

A claims-based analysis of infants with IS who were treated with RCI demonstrated a resource use benefit associated with early treatment (within 30 days of diagnosis) compared with later treatment (≥30 days after diagnosis) [53]. In particular, early use of RCI led to 3.8 fewer outpatient visits (99% confidence interval [CI] −6.7 to −0.7; $p = 0.002$) and 4.2 fewer visits for all health services combined (99% CI −7.9 to −0.4; $p = 0.005$).

Multiple Sclerosis Relapses

An economic analysis of patients with MS relapses who had received prior treatment with

IV methylprednisone demonstrated decreased healthcare utilization for RCI therapy compared with the two therapies that are used most often for the treatment of MS relapse, IVIG and PMP [54]. Over a 12-month period, the RCI group had 0.2 fewer hospitalizations (95% CI −0.3 to −0.1; $p = 0.01$), 15 fewer outpatient services (95% CI −20 to −10; $p < 0.0001$), 3.7 fewer days in hospital (95% CI −4.8 to −1.1; $p = 0.01$), 0.19 fewer rehabilitation and long-term care facilities services (95% CI −0.26 to −0.12; $p < 0.001$), and 3.2 fewer overall healthcare services (95% CI −5.2 to −1.1; $p = 0.003$) while incurring similar total healthcare costs (US$106,400 vs. US$109,400; $p = 0.74$). Favorable cost outcomes for RCI compared with IVIG or PMP also were observed in a 24-month analysis (inpatient costs US$17,400 lower, $p = 0.03$; outpatient costs US$121,000 lower, $p < 0.0001$; total costs US$33,400 lower, $p = 0.13$). Although drug costs for RCI treatment were greater than for IVIG or PMP, they were offset by decreases in inpatient and outpatient costs (93% medication cost offset at 12 months; 132% offset at 24 months).

Rheumatoid Arthritis

In patients with RA, treatment with RCI may result in reduced healthcare utilization and decreased use of other RA medications. The HealthCore Integrated Research Database, a large healthcare claims database containing data for 36.8 million commercial health plan members, was used to retrospectively examine healthcare utilization and costs in patients with RA before and after initiating treatment with RCI [55]. Of 6190 eligible RA patients, 180 patients had received RCI. Treatment with RCI was associated with substantial reductions in the use of corticosteroids, biologics, and non-biologic DMARDs. The RCI cohort also had lower rates of hospitalization after treatment initiation compared with before (all-cause hospitalizations: 42 preinitiation vs. 25 postinitiation per 1000 patient-years, $p < 0.01$; RA-related hospitalizations: 13 vs. 4 per 1000 patient-years, $p < 0.01$), emergency department visits (all-cause visits: 43 vs. 23 per 1000 patient-years, $p = 0.04$; RA-related visits: 8 vs. 1 per 1000 patient-years, $p < 0.01$), and outpatient services (all-cause encounters: 56 vs. 47 per patient-year, $p < 0.01$; RA-related encounters: 10 vs. 5 per patient-year, $p < 0.01$). Patients incurred higher RA-related drug costs after RCI initiation compared with before initiation (US$4379 vs. US$273 per patient per month [PPPM], $p < 0.01$). However, RA-related medical costs were substantially lower after RCI initiation than before (US$93 vs. US$658 PPPM, $p < 0.01$) because of fewer inpatient, outpatient, and emergency department services. The reduction in medical costs offset RCI drug costs by 14–30%.

Dermatomyositis and Polymyositis

An economic analysis of 2009–2014 US claims data for patients with DM/PM found a decrease in healthcare utilization in patients treated with RCI [56]. Patients treated with RCI ($n = 132$), IVIG ($n = 1150$), or rituximab ($n = 562$) were propensity score-matched on demographic and clinical characteristics and prior medical resource utilization. The RCI group had fewer mean hospitalizations than the IVIG group (0.09 vs. 0.17 PPPM; $p = 0.049$), shorter mean length of stay (3.24 vs. 4.55 days; $p = 0.004$), and fewer hospital outpatient department visits (0.60 vs. 1.39 PPPM; $p < 0.001$) and physician office visits (2.01 vs. 2.33 PPPM; $p = 0.035$), but similar numbers of emergency department visits (0.04 vs. 0.05 PPPM; $p = 0.472$). RCI patients also had fewer hospital department outpatient visits than patients receiving rituximab or IVIG + rituximab and shorter hospital length of stay. Total mean nonmedication costs were significantly lower in the RCI group than in the IVIG group (US$2126 vs. US$3964; $p < 0.001$), rituximab group (US$2008 vs. US$2607; $p = 0.018$), and IVIG + rituximab group (US$1234 vs. US$4858; $p < 0.001$).

Systemic Lupus Erythematosus

In an analysis of healthcare utilization in patients with SLE, 9944 eligible patients (age ≥18 years) were identified using US commercial

claims data for 2006–2015 [57]. Of this group, 29 patients had initiated RCI therapy, with the drug initiated an average of 23 months after diagnosis of SLE. Healthcare utilization in the period before RCI initiation (average duration, 23 months) and the period after initiation (average follow-up, 24 months) was compared. Decreases in mean number of hospitalizations and ED visits PPPM were observed postinitiation. Drug costs increased from US$905 PPPM to US$7743 PPPM postinitiation; however, SLE-related medical costs decreased from US$3301 PPPM to US$893 PPPM ($p = 0.02$), primarily owing to lower hospitalization costs, offsetting approximately one-third of the increase in drug costs.

Multiple Rheumatologic Conditions

In an analysis of a pooled population of patients with various rheumatologic conditions (RA, $n = 1269$; SLE, $n = 874$; DM/PM; $n = 606$), the proportions of patients who used corticosteroid therapy were significantly lower after RCI initiation (reduced from 67% preindex to 54% postindex for RA, from 73% to 58% for SLE, and from 76% to 58% for DM/PM; $p < 0.05$ for all comparisons) [58]. Furthermore, the proportions of patients who were receiving biologics and DMARDs were also significantly lowered after initiation of RCI treatment.

General clinical practice is to use RCI as a late-line therapy in patients with autoimmune flares or whose disease has been inadequately controlled with first-line therapies. Taken together, these various retrospective analyses suggest that treatment with RCI is associated with reduced healthcare utilization in patients with moderate to severe disease progression. The lower healthcare utilization may reflect an improvement in disease control, corresponding to the improvements in clinical outcomes observed in the studies summarized above, and warrants additional research.

CONCLUSION

RCI is used to treat several serious and rare autoimmune conditions. There has been a renewed interest in RCI, partly because of recent progress in understanding the mechanisms by which RCI modulates immune responses. Currently, RCI is considered first-line therapy for IS; for other autoimmune disorders reviewed here it is used primarily as later-line therapy in patients experiencing a disease exacerbation or as adjunctive or maintenance therapy in selected patients who do not respond to or are intolerant of conventional treatment.

More than two dozen clinical trials of RCI in the treatment of MS relapses, symptomatic sarcoidosis, SLE, RA, optic neuritis, proteinuria, DM, and other diseases and conditions are currently registered in the National Institutes of Health clinical trials database (http://www.ClinicalTrials.gov); it is anticipated that this research will greatly improve our understanding of the appropriate use of RCI. The large burden that autoimmune diseases impose on patients, families, healthcare systems, and society warrants continued research to expand the knowledge base of effective therapeutic options for these challenging disorders.

The studies summarized in this review support the potential clinical efficacy of RCI across several autoimmune diseases and disorders. In addition, retrospective analyses suggest that treatment with RCI for RA, SLE, and DM/PM was associated with substantial reductions in the use of corticosteroids, biologics, and nonbiologic DMARDs. Furthermore, initiation of RCI therapy may be associated with subsequent lower healthcare utilization, including decreases in hospitalizations, hospital length of stay, and outpatient visits. The evidence suggests that RCI may improve inflammatory and autoimmune disease control and patient quality of life, particularly in complex patients, and yield healthcare cost savings that demonstrate the medicine's value.

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