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REVIEW

Acthar Gel (RCI): A Narrative Literature Review of Clinical and Economic Evidence

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Abstract: Acthar® Gel (repository corticotropin injection [RCI]) is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides used to treat patients with serious and rare inflammatory and autoimmune conditions. This narrative review summarizes the key clinical and economic findings among 9 indications: infantile spasms (IS), multiple sclerosis (MS) relapses, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis and polymyositis (DM/PM), ocular inflammatory diseases (primarily uveitis and severe keratitis), symptomatic sarcoidosis, and proteinuria in nephrotic syndrome (NS). Key studies of clinical efficacy and healthcare resource utilization and cost from 1956 to 2022 are discussed. Evidence supports the efficacy of RCI across all 9 indications. RCI is recommended as first-line treatment for IS and is associated with improved outcomes for the other 8 indications, including increased recovery rates in MS relapse; improved disease control in RA, SLE, and DM/PM; real-world effectiveness in patients with uveitis and severe keratitis; improved lung function and reduced corticosteroid use in symptomatic sarcoidosis; and increased rates of partial remission of proteinuria in NS. For many indications, RCI may improve clinical outcomes during exacerbations or when conventional treatments have failed to show a benefit. RCI is also associated with a reduction in the use of biologics, corticosteroids, and disease-modifying antirheumatic drugs. Economic data suggest RCI is a cost-effective, value-based treatment option for MS relapse, RA, and SLE. Other economic benefits have been demonstrated for IS, MS relapses, RA, SLE, and DM/PM, including reduced hospitalizations, lengths of stay, inpatient and outpatient services, and emergency department visits. RCI is considered safe and effective and features economic benefits for numerous indications. Its ability to control relapse and disease activity makes RCI an important nonsteroid treatment option that could help preserve functioning and well-being among patients with inflammatory and autoimmune conditions.

Keywords: dermatomyositis and polymyositis, multiple sclerosis relapse, nephrotic syndrome, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus

Plain Language Summary

- Acthar® Gel (RCI) is approved by the US Food & Drug Administration for the treatment of several autoimmune disorders and medical conditions known to cause inflammation. This includes but is not limited to infantile spasms, multiple sclerosis relapses, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and polymyositis, primary uveitis and severe keratitis, sarcoidosis, and proteinuria in nephrotic syndrome.
- This article summarizes findings from 70 years of research on RCI among 9 specific medical conditions. It includes studies on whether RCI improves patients' symptoms and functioning as well as studies on its safety and side effects. The review also addresses research on whether using RCI results in economic benefits.
- Our review found that, among all 9 medical conditions studied, RCI has been effective in reducing symptoms, improving functioning and well-being, reducing disease relapse, and/or increasing disease remission. We also found that for medical conditions such as multiple sclerosis relapses and rheumatoid arthritis, RCI was associated with reduced spending and less use of health care resources. This included a reduction in admissions to the emergency department and length of inpatient hospitalizations.

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- This review shows that decades of research and clinical experience strongly support the use of RCI as safe and effective in reducing exacerbation or acting as maintenance therapy for the conditions studied here and that it offers patients with autoimmune and inflammatory diseases a chance to alleviative symptoms, which in turn may improve their quality of life.

Introduction

Acthar® Gel (repository corticotropin injection [RCI]) is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) analogs and other pituitary peptides supplied as a sterile preparation in 16% gelatin to provide a prolonged release after intramuscular or subcutaneous injection. For more than 70 years, RCI has been used as a US Food and Drug Administration (FDA)–approved therapy to treat patients with serious and rare conditions. Treatment with RCI has also been selectively prescribed to small patient populations and used as later-line treatment for patients who require an alternative to other therapies. RCI is currently approved for use in 19 indications.[1]

The aim of this narrative review is to summarize the clinical and economic evidence to support the efficacy, effectiveness, safety, and economic value of RCI for the following select indications: infantile spasms (IS), multiple sclerosis (MS) relapses, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis and polymyositis (DM/PM), ocular inflammatory diseases (primarily uveitis and severe keratitis), symptomatic sarcoidosis, and proteinuria in nephrotic syndrome (NS). Key studies of clinical efficacy and health care resource utilization (HCRU) and cost from 1956 to 2022 are discussed. This review includes previously conducted studies and does not summarize any new human or animal studies performed by any of the investigators.

Indications

RCI is indicated as monotherapy for the treatment of IS in infants and children under 2 years of age[1] and for MS relapses in adults;[1] controlled clinical trials have demonstrated its efficacy in speeding the resolution of acute exacerbations of MS during relapses. However, there is no evidence that it affects the ultimate outcome or natural history of the disease. It is indicated as adjunctive therapy for short-term administration in PsA; RA, including juvenile RA; and ankylosing spondylitis.[1] Other indications include treatment during an exacerbation or as maintenance therapy in selected cases of SLE; treatment during an exacerbation or as maintenance therapy in selected cases of DM/PM; symptomatic sarcoidosis; and inducing a diuresis or a remission of proteinuria in NS without uremia of the idiopathic type or secondary to lupus erythematosus.[1] Finally, RCI is indicated for severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.[1]

The safety profile of RCI has been demonstrated over many years of clinical use.[1] According to published studies, RCI may have different adverse effects (AEs) than glucocorticoids,[2] and thus a February 2021 label change for RCI removed previous language from the highlights page stating that common adverse reactions for RCI are similar to those for corticosteroids.[1–3] The most commonly reported postmarketing adverse reactions for RCI include injection site reaction, asthenic conditions (including fatigue, malaise, asthenia, and lethargy), fluid retention (including peripheral swelling), insomnia, headache, and an increase in blood glucose.

Tables S1-S8 summarize the clinical benefits, economic benefits, and potential AEs of RCI among the 9 indications discussed in detail below.

Infantile Spasms (IS)

IS is a rare seizure disorder that occurs in young children, usually under 1 year of age.[4,5] Infantile spasms are associated with significant morbidity, including developmental delay, autism, and intellectual disability and other severe developmental outcomes.[5,6]

RCI is the only ACTH-containing preparation approved by the FDA for IS, and it is the most prescribed treatment for IS in the United States (US). (Data on File - Ref-05625. Mallinckrodt Pharmaceuticals; Data from Symphony Health, Personal Communication, December 13, 2021). RCI has been recommended as a first-line therapy for IS by the American Academy of Neurology and the Child Neurology Society in their practice guideline on the treatment of IS in children, and this recommendation was reaffirmed in the 2017 Quality Measure Set from the American Academy of

Neurology and Child Neurology Society.[4,7] RCI has been approved by the FDA as monotherapy for the treatment of IS in infants and children under 2 years of age for more than a decade.[1] Evidence for the benefits of RCI in IS is presented in Table S1.

Clinical Benefits

Clinical trials and retrospective chart reviews have consistently shown seizure cessation or reductions in seizure frequency in patients with IS who are treated with RCI.[8–12] Several clinical studies have demonstrated higher response rates in patients with IS who were treated with RCI vs other therapies (eg, oral corticosteroids or vigabatrin).[13–16]

Early (ie, 2 weeks) and sustained (ie, 3 months) clinical remission and resolution of hypsarrhythmia in IS has been demonstrated with RCI in a US multicenter, prospective, real-world study of 230 patients with IS who were treated with RCI, oral corticosteroids, vigabatrin, or nonstandard therapies.[13] Fifty-five percent of infants who received RCI (53/97) as initial treatment responded at 3 months, compared with 39% who received oral corticosteroids, 36% who received vigabatrin, and 9% who received other therapy ($p<0.001$). The response rate in the RCI group was significantly higher than in the vigabatrin group (p=0.038) and numerically higher than in the oral corticosteroids group ($p=0.06$). The study was not a head-to-head trial.

In the treatment of IS, the most common adverse reactions are increased risk of infections, convulsions, hypertension, irritability, and pyrexia.[1]

Economic Benefits

RCI has been shown to reduce HCRU in patients with IS, and earlier treatment with RCI may lead to better economic outcomes.[17] Reduced HCRU in patients with IS after treatment with RCI was reported in a survey of 101 neurologists and internal medicine physicians across the US.[17] Physicians reported a significant decrease in HCRU 3 months post–RCI compared with 3 months pre-RCI in emergency department (ED) visits ($p<0.001$) and hospitalizations ($p<0.001$). Earlier use of RCI use was associated with, on average, 3.8 fewer outpatient services (and 4.2 fewer total health services).

In a retrospective claims database study (N=252), patients with IS who were treated with RCI within 30 days of their diagnosis required fewer outpatient services and fewer total healthcare services than patients who were prescribed RCI later in their disease process (>30 days after diagnosis). Early RCI use was associated with, on average, 3.8 fewer outpatient services (99% CI, 0.7–6.7) and 4.2 fewer total health services (99% CI, −7.9 to −0.4).[18]

Summary

Clinical studies and retrospective chart reviews of RCI demonstrate statistically significant improvements in IS, such as seizure cessation and/or reductions in seizure frequency. Several studies indicate that RCI–treated patients may have higher response rates than patients treated with alternative therapies, such as corticosteroids or vigabatrin. The safety profile of RCI in the IS population has been demonstrated over many years of clinical use.

RCI was shown to provide economic benefits for appropriate patients with IS. Economic studies indicate that RCI treatment for IS can lead to reductions in HCRU, and earlier treatment with RCI may lead to better economic outcomes.

Multiple Sclerosis Relapse

MS is a complex and chronic demyelinating autoimmune neurological disorder.[19] Relapses among MS patients are associated with significant functional impairment and decreased quality of life (QoL), and residual symptoms often persist and lead to sustained disability despite therapy.[20,21] Additional data for the treatment of MS relapse with RCI are provided by a prospective observational registry,[22] a retrospective claims study,[23] and a retrospective case series.[24] Evidence for the benefits of RCI in MS relapse is presented in Table S2.

Clinical Benefits

RCI is indicated for the treatment of acute exacerbations of MS in adults.[1] Controlled clinical trials have shown that RCI increases recovery rates and improves disability scores in patients with acute MS relapse.[25] In the multicenter, randomized, double-blind, placebo-controlled, parallel-group OPTIONS trial, 35 patients with relapsing-remitting MS

who were experiencing an acute relapse that was not adequately responding to high-dose corticosteroids were randomized 1:1 to RCI 80 U or matching placebo daily for 14 days.[25] Sixty-one percent of patients who were receiving RCI and 11.1% of patients who were receiving placebo achieved the primary objective of patients showing substantial improvements on the Expanded Disability Status Scale and qualitative Clinical Global Impression-Improvement scales compared with placebo. The incidence of treatment-emergent AEs (TEAEs) was similar between RCI (77.8%) and placebo (70.6%) groups, with no serious AEs or deaths in the RCI group.[25]

Economic Benefits

Fewer hospitalizations and outpatient services as well as lower inpatient hospitalization and outpatient costs have been associated with RCI treatment compared with alternative therapies for MS relapse, such as plasmapheresis (PMP) or intravenous immunoglobulin (IVIG).[23,26–28] In a claims database analysis, a lower mean total of relapses, inpatient stays, and outpatient visits were reported in RCI–treated patients with MS (n=232) compared with PMP/IVIG-treated patients with MS (n=141), during a 12-month follow-up period.[23]

In another claims database analysis, HCRU at 12 months was reduced significantly in RCI–treated patients compared with PMP- or IVIG-treated patients.[26] In unadjusted 12-month outcomes, patients treated with RCI had on average 0.4 fewer hospitalizations (p=0.0002), 17 fewer outpatient services (p<0.0001), and 3.3 fewer length of stay (LOS) days (p=0.01). Inpatient and outpatient costs were significantly lower for patients treated with RCI ($15,300 and $54,100 lower; p=0.001 and p<0.0001, respectively) than for those treated with PMP or IVIG. Unadjusted medication costs for RCI were $74,900 higher than costs for PMP or IVIG; however, similar average total adjusted costs were associated with RCI ($106,400) and PMP or IVIG ($109,400). Overall, the medication costs for RCI were offset by 93% (among the cohort with 12 months of follow-up) and 132% (among the cohort with 24 months of follow-up) by the relative decrease in inpatient and outpatient costs for the RCI group.[26]

An analysis using costs obtained from Truven Health Analytics MarketScan® Commercial Claims and Encounters Database found that the total annual cost of treatment for relapses was similar for RCI ($122,946) and PMP/IVIG ($126,412).[27] However, the response rate with RCI (78.3% to 96.9%, depending on source) was higher than with PMP/IVIG (45.9% to 56.0%), so the range of cost per response was lower for RCI ($126,879 to $157,019) than for PMP/IVIG ($225,736 to $275,407).

Another analysis estimated the cost effectiveness of RCI for the treatment of acute exacerbations in MS compared with PMP and IVIG from the US payer and societal perspectives.[28] Considering the payer perspective over 1 year, use of RCI resulted in an incremental quality-adjusted life-years (QALY) gain of 0.115 at an additional average cost of $4839, which translates to an incremental cost-effectiveness ratio (ICER) of $42,078 compared with PMP. At 2 and 3 years, use of RCI resulted in an average cost savings of $6827 and $18,551 and an average QALY gain of 0.241 and 0.368, respectively, compared with PMP. Compared with IVIG, RCI resulted in annual cost savings of $79,867 to $275,954, an incremental QALY gain of 0.120 to 0.376 at Years 1 to 3. From a societal perspective, use of RCI resulted in lower costs and positive incremental QALYs for both PMP and IVIG for all 3 years.[28]

Summary

A randomized controlled trial of RCI in patients with MS demonstrated statistically significant improvements in recovery rates after MS relapse. The safety profile of RCI in the MS population has been demonstrated over many years of clinical use. Data from a claims database analysis indicate decreased resource use and similar overall costs for RCI vs IVIG or PMP treatment, supporting the economic value of RCI in the treatment of MS relapse. RCI was shown to be a cost-effective, value-based treatment option for appropriate patients with MS and is included in both the Multiple Sclerosis Association of America's and National Multiple Sclerosis Society's treatment pathways for relapses of MS.[29,30]

Rheumatoid Arthritis

RA is an autoimmune disease that manifests as inflammation and hyperplasia of the synovial membrane surrounding the joints. Because of the presence of systemic inflammation and immune dysfunction, RA is also associated with numerous

extra-articular comorbidities. RA imposes a significant humanistic and economic burden on afflicted individuals, their families, and society.[31,32] Evidence for the benefits of RCI in RA is presented in Table S3.

Clinical Benefits

RCI is approved for adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in RA. Patients with active RA who had inadequate response to treatment with glucocorticoids and 1 or 2 disease-modifying antirheumatic drugs (DMARDs) are appropriate candidates for RCI therapy.[2] Three prospective clinical studies evaluated the efficacy and safety of RCI as adjunctive therapy in patients with RA.[2,33,34]

In a 12-week, single-center, prospective, open-label, interventional study, 80 U RCI was administered subcutaneously (SC) every 72 hours for 12 weeks as add-on therapy to patients with RA (N=8) who had not responded adequately to at least 3 biological agents.[33] All patients continued to receive methotrexate along with their current biologic. The primary endpoint of decreased swollen (p=0.0004) and tender (p=0.0047) joint counts was achieved. AEs reported included injection-site reaction, hypoglycemia, hip pain, development of allergies, pneumonia, atrial fibrillation, fibromyalgia, and hypertension.[33]

A 2-part, randomized, placebo-controlled, multicenter withdrawal study evaluated the efficacy, safety, and tolerability of RCI in 259 subjects with active RA despite treatment with prednisone (or an equivalent) and DMARDs.[2,34] The primary efficacy endpoint, DAS28-ESR <3.2 at Week 12 in part 1 (open label), was achieved by 63% (163/259) of patients (p<0.001).

In part 2 (double blind), patients who achieved DAS28-ESR <3.2 at Week 12 in part 1 were randomly assigned to continue RCI or switch to placebo.[2,34] After an additional 12 weeks, 61% of 77 patients who continued treatment with RCI maintained DAS28-ESR <3.2 compared with 42% of 76 patients who switched to placebo (p=0.019). In the same population, 86% of 77 patients who were receiving RCI and 66% of 76 patients who received placebo maintained a Clinical Disease Activity Index (CDAI) score ≤10 at Week 24 (p=0.004). There were few differences in ACR20, ACR50, and ACR70 between treatment groups during part 2. Improvements in patient-reported outcomes were sustained with RCI continuation or withdrawal through Week 24. During the open-label period, 43 subjects (16.6%) reported treatment-related AEs. During the double-blind period, 9 patients (11.7%) in the RCI group and 10 (13.0%) in the placebo group reported treatment-related AEs. No patients died during the study.[2,34]

Real-world effectiveness of RCI in patients with RA was evaluated in 3 separate studies from retrospective medical chart reviews of rheumatology practices.[35–37] In one study of RCI treatment patterns and physician impression of change among patients with RA, SLE, or DM/PM, 78% of RA patients (n=32) had a rating of "improved" on physicians' impression of change.[35] A retrospective analysis of electronic medical records data of patients with RA (n=114) found RCI was associated with clinically meaningful reductions in disease activity and severity, including significant improvements in joint swelling and tenderness as well as pain.[36]

Economic Benefits

RCI has been shown to reduce HCRU and costs in patients with RA who initiate RCI therapy.[38–40] In a retrospective claims database analysis that included 180 patients with RA who initiated RCI therapy, patients had significantly lower all-cause and RA-related per-patient-per-month (PPPM) medical costs at the postinitiation period vs the preinitiation period (both values, p<0.01).[39] Costs were driven by lower PPPM hospitalization costs.

In another claims database analysis, the proportion of patients with RA who used prednisone was significantly lower after RCI initiation. Use of biologics and DMARDs in patients with RA was also significantly reduced after RCI initiation.

An individual-level microsimulation was developed to estimate the cost effectiveness of RCI vs standard of care (SoC) in patients with active RA despite aggressive treatment.[40] Over 2 years, RCI had an incremental QALY gain of 1.591 and incremental cost of $183,965 and $117,443 from payer and societal perspective, respectively, resulting in an ICER of $115,629/QALY and $73,817/QALY compared with SoC. Over 3 years, RCI had an incremental QALY gain of 2.336 and incremental cost of $202,315 and $104,506 from payer and societal perspective, respectively, resulting in an ICER of $86,607/QALY and $44,737/QALY compared to SoC.[40]

Summary

Clinical and real-world studies have evaluated the efficacy, effectiveness, and safety of RCI as adjunctive therapy in patients with RA. A claims database analysis demonstrated lower inpatient and ED visits and associated costs for patients with RA after RCI initiation. RCI was shown to be a cost-effective, value-based treatment option for appropriate patients with RA.

Systemic Lupus Erythematosus

SLE is a systemic illness with multiple end-organ involvement characterized by intermittent relapses that can involve any organ or system overlaid on a backdrop of relative quiescence.[41] The mean total cost for the overall population of SLE patients in the US has been estimated to be $20,924 (2004 US dollars), including the direct costs associated with providing health care and the costs associated with changes in work productivity.[42] Evidence for the benefits of RCI in SLE is presented in Table S4.

Clinical Benefits

RCI is indicated for treatment during an exacerbation or as maintenance therapy in selected cases of SLE. The safety and efficacy of RCI in the treatment of SLE has been examined in 2 randomized, double-blind trials and 1 single-center trial.

A multicenter, randomized, double-blind, placebo-controlled trial enrolled 172 adults with active SLE who received RCI (n=84) or placebo (n=85).[43] Patients who were treated with RCI showed greater reductions in 28 swollen/tender joint counts and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity scores at Week 16 than patients receiving placebo.[43] Post hoc analyses demonstrated greater improvements with RCI in the pain, planning, and fatigue domains than with placebo at multiple time points in patients with higher disease activity and/or in responders.[44]

In the safety population, more patients who were treated with RCI reported AEs than patients who were given placebo (61/86 vs 55/86).[43] The most common AEs reported by patients who were treated with RCI included upper respiratory tract infection, insomnia, headache, hypertension, and urinary tract infection. Fewer patients in the RCI–treated group than in the placebo-treated group reported serious adverse events; these included SLE, herpes zoster, and NS. The AEs of SLE, drug hypersensitivity, and NS resulted in study discontinuation for RCI-treated patients.

In a pilot study with an open-label extension, RCI was evaluated in 38 patients with persistently active SLE who failed to respond to moderate-dose corticosteroids, with double-blind randomization to RCI 40 IU (n=13), RCI 80 IU (n=13), or placebo (n=12).[45] Patients treated with RCI in both phases had a durable response to therapy over 52 weeks, whereas those initially treated with placebo experienced improvements in disease activity during the open-label extension that were generally similar to the improvements with RCI from the blinded phase of the trial.[45,46]

The overall incidences of TEAEs and treatment-related TEAEs in the combined RCI and combined placebo groups were similar and were mild or moderate in severity for most cases.[45,46] The most reported AE was weight gain, which occurred in 7 patients (19.4%), with similar frequencies in each group. The overall incidence of infections was higher in the RCI groups (23.1% in each group) than in the combined placebo group (9.1%), but there were no other differences in AE profiles between the groups.[45,46] During the study course, there were no clinically significant changes in physical examination findings or vital signs including blood pressure or clinical laboratory tests.[45,46]

After treatment with RCI, female patients with SLE and a disease flare (N=10) showed statistically significant improvements in the SLE Disease Activity Index 2000 scores at Day 28 ($p<0.01$) and improvements in the Physician Global Assessment ($p<0.01$), Patient Global Assessment ($p\leq0.01$), Functional Assessment of Chronic Illness Therapy-fatigue ($p<0.01$), and ESR ($p\leq0.03$).[45,46] No treatment-related serious or unexpected AEs were observed.[47]

Economic Benefits

In a claims database analysis that examined real-world treatment patterns and economic characteristics of patients with SLE initiating RCI (N=29), patients with SLE used significantly fewer outpatient services ($p<0.01$) and fewer prescription fills ($p<0.01$) during the postinitiation vs the preinitiation period.[39] During the postinitiation period compared with

the preinitiation period, the study found a 20.2% reduction in the rate of all-cause hospitalizations and a 12.6% reduction in the rate of all-case ED visits; however, the results were not statistically significant. Patients with SLE had significantly reduced PPPM all-cause hospitalization costs ($3192 vs $799, p=0.04) and increased PPPM prescription costs ($905 vs $7443, p<0.01) after initiating RCI.

In another claims database analysis, the proportion of patients with SLE who used prednisone was significantly lower after RCI initiation (reduction from 6 months preinitiation to 6 months postinitiation = 73% to 58%, p<0.05). Use of biologics and DMARDs in patients with SLE was also reduced after RCI initiation.[38]

In the base case scenario, RCI was cost effective at ≥2 years from the US payer and societal perspectives at a willingness-to-pay threshold of $150,000 per QALY.[48] From the payer perspective, RCI was cost effective after the first year at a threshold of $150,000 per QALY; ICER was $133,110/QALY at 2 years and $94,818/QALY at 3 years compared with the SoC. From the societal perspective, RCI was cost effective after the first year at a threshold of $100,000 per QALY; ICER was $70,827/QALY at 2 years and $32,525/QALY at 3 years compared to the SoC.[48]

Summary

Although the randomized, double-blind trial of RCI versus placebo did not meet their primary endpoint, several disease measures showed significant improvements with RCI compared with placebo. In that trial of patients with moderate-to-severe SLE, the findings supported the utility of RCI for treating persistently active SLE.[44] Treatment of SLE with RCI has been shown to reduce HCRU (inpatient and ED visits) and lower associated costs. RCI was shown to be a cost-effective, value-based treatment option for appropriate patients with SLE.

Dermatomyositis/Polymyositis

DM and PM are uncommon inflammatory myopathies characterized by muscle inflammation and weakness proximal to the trunk. DM/PM is associated with a substantial economic burden in the US population, ranging from $533 million to $702 million per year.[49] Patients with DM/PM use significantly more health care resources and experience significantly greater work loss compared with matched controls (p<0.001).[50] Evidence for the benefits of RCI in DM and PM is presented in Table S5.

Clinical Benefits

RCI is indicated for treatment during an exacerbation or as maintenance therapy in selected cases of systemic DM/PM. An interim observational case study of patients (N=24) in the RCI in Dermatomyositis and Polymyositis Treatment (ADAPT) registry demonstrated that patients with DM had a 57% response rate to RCI treatment, whereas those with PM had a 59% response rate. Patients who responded to treatment had a higher mean treatment duration (9.7 months) than nonresponders, whose mean treatment duration was 3.5 months (p<0.0001).[51] The efficacy and safety of RCI in patients with DM and PM have also been evaluated in a small clinical study.[52]

Economic Benefits

HCRU and costs have been evaluated for RCI treatment compared with IVIG and/or rituximab. In a retrospective study of claims from 3 commercial health insurance databases,[53] patients with a primary diagnosis of DM/PM who were treated with RCI had lower PPPM nonmedication medical resource utilization and costs than those treated with IVIG and/or rituximab. Patients treated with RCI had significantly fewer PPPM hospitalizations (p=0.049), shorter LOS (p=0.004), fewer PPPM hospital outpatient department (HOPD) visits (p<0.001), and fewer PPPM physician office visits (p=0.035) than IVIG-treated patients.[53] RCI–treated patients had fewer PPPM HOPD visits (p<0.001) than rituximab-treated patients. Patients treated with RCI had shorter LOS (p<0.001) and fewer PPPM HOPD visits (p<0.001) than patients treated with IVIG + rituximab.[53] Total nonmedication PPPM costs were 23% to 75% lower for patients treated with RCI compared with IVIG ($2126 vs $3964; p<0.001), rituximab ($2008 vs $2607; p=0.018), and IVIG + rituximab ($1234 vs $4858; p<0.001).[53]

In another claims database analysis, the proportion of patients with DM/PM who used any corticosteroids was significantly lower after RCI initiation (reduction from 6 months preinitiation to 6 months postinitiation = 76% to 58%;

$p<0.05$).[38] Use of DMARDs was also reduced after RCI initiation. Among patients with DM/PM who had taken corticosteroids consistently 24 weeks before RCI initiation (n=131), the mean prednisone dose trended lower (25% reduction, not statistically significant), comparing 12 weeks before and after RCI initiation.

Summary

Observational data support the effectiveness and safety of RCI treatment for DM/PM. In the ADAPT registry analysis, 58.3% of patients (14/24) responded to RCI treatment. RCI was shown to provide economic benefits for appropriate patients with DM/PM. Economic data demonstrate that patients with DM/PM treated with RCI have significantly lower PPPM nonmedication HCRU and costs than patients treated with IVIG and/or rituximab.

Ocular Inflammatory Diseases

Uveitis is an ocular inflammatory disease that affects the uveal tract and adjacent structures including the sclera, cornea, vitreous humor, retina, and optic nerve head.[54] If left untreated, uveitis can lead to poor visual outcomes including blindness.[55] A claims database analysis that examined clinical outcomes, health care resource use, and cost in patients with noninfectious inflammatory eye disease (ie, uveitis and other intraocular inflammations) showed that patients with noninfectious inflammatory eye disease were more likely than controls without noninfectious inflammatory eye disease to experience ocular complications.[56,57]

Delphi panel consensus recommendations published in 2021 indicated that RCI may be an option for intermediate noninfectious uveitis, posterior noninfectious uveitis, panuveitis, and ocular cicatricial pemphigoid.[58]

Patients with noninfectious intermediate, posterior, or panuveitis experience greater direct (medical and pharmacy) (all $p<0.0001$) and indirect costs (associated with disability and medically related absenteeism) than matched controls without uveitis (all $p<0.05$).[59] The average annual cost for patients with noninfectious inflammatory eye disease is between $13,728 and $32,268 (in 2009 dollars), or 3.1 to 8.3 times higher than the cost for patients without noninfectious inflammatory eye disease, according to a retrospective database study using data from 2003 to 2009.[60] Payers incur $15,646 in annual health care costs per patient with noninfectious inflammatory eye disease, which is 40% higher than costs for matched controls. The areas with the largest differences were prescription drugs ($2251) and outpatient/physician office visits ($1226). Furthermore, patients with noninfectious inflammatory eye disease had 3.5 additional days of work loss compared with matched controls.[57] Health care expenditure for high-cost patients (top 20%) with noninfectious inflammatory eye disease averaged $59,873 and was driven by inpatient admissions, ED visits, and prescription drug use.[61] Evidence for the benefits of RCI in ocular inflammatory diseases is presented in Table S6.

Clinical Benefits

RCI is indicated for the treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.

One nonrandomized, prospective trial evaluated RCI for refractory severe noninfectious keratitis.[62,63] After 12 weeks, significant improvements were reported in the Impact of Dry Eye on Everyday Life score, visual analog scale for burning/stinging and eye discomfort/pain, and Ocular Discomfort Score. One-third of patients experienced ≥1 TEAE.

The real-world effectiveness of RCI in patients with uveitis was assessed in a retrospective medical record review of 91 patients.[64] After treatment with RCI, 84% (n=76) of 91 patients were "improved" and 16% (n=15) were the "same" according to physicians. Physicians' assessment of patients' improved current status showed that 86% (n=78) had improvements in vision and 27% (n=25) of patients reported improvements in pain. No patient worsened while receiving RCI.[64] Most patients were receiving multiple therapies; thus, the clinical outcomes may not be solely attributable to RCI.[64]

Economic Benefits

Currently, no economic studies have evaluated the economic impact of RCI in the treatment of ocular inflammatory diseases, including uveitis.

Summary

RCI has been used since 1952 to treat ocular inflammatory disease, and it continues to have a place in therapy for these conditions. RCI showed real-world effectiveness in uveitis, with 84% (76/91) of patients in 1 study improving after treatment, and it also significantly reduced the signs and symptoms of refractory severe noninfectious keratitis, with 41%–65% of patients (n=36) showing ≥20% improvement at weeks 2, 4, 6, and 12.[62] The economic benefits of RCI in patients with ocular inflammatory diseases have yet to be established.

Symptomatic Sarcoidosis

Symptomatic sarcoidosis is a multisystem granulomatous disease characterized by the formation of immune granulomas in various organs such as the lungs and the lymphatic system.[65] Sarcoidosis is associated with a significant burden to affected patients because the symptoms of the disease are disabling and impair QoL.[66]

A U.S. modified Delphi panel included RCI as an appropriate option for patients with advanced symptomatic sarcoidosis that is not controlled with other medications,[67] and the 2021 European Respiratory Society Clinical Practice Guidelines on sarcoidosis note the use of RCI as an alternative treatment for patients with sarcoidosis.[68] Evidence for the benefits of RCI in symptomatic sarcoidosis is presented in Table S7.

Clinical Benefits

The safety and efficacy of RCI for the treatment of sarcoidosis was evaluated in a prospective clinical study[69] and 2 retrospective chart reviews.[70,71] A single-blind prospective study compared 2 doses of RCI in patients with advanced pulmonary sarcoidosis (N=16).[69] At Weeks 7 and 24, RCI was associated with a significant reduction in the dosage of prednisone, irrespective of dosage received, in addition to improvements in health-related QoL.[69] No significant difference was noted in patient-reported prednisone toxicity including changes in moodiness, appetite, or bruising. None of the 6 patients who had elevated HbA1c levels at study entry had their HbA1c level fall to within normal range by study end.[69]

In a retrospective medical records study of 302 patients with symptomatic sarcoidosis, 95% of patients showed improvement when treated with RCI, per physician reports.[70] The most commonly reported improvements were in overall symptoms (73%), lung function (38%), inflammation (33%), reduction or discontinuation of corticosteroid use (32%), and patient QoL (32%). Approximately half of patients had improvements in ≥2 symptom categories.

In a post hoc analysis of the 302 patients included in the Chopra et al 2019 chart review, the most influential predictor of current health status was complete compliance to treatment with RCI, giving significantly better odds of improvement vs partial compliance to RCI treatment (odds ratio [OR] =10.64; 95% CI, 1.35–83.86).[72] Patients with complete compliance to RCI also had significantly higher odds of improvement in overall symptoms vs those with partial compliance (OR=2.47; 95% CI, 1.23–4.96). In addition, patients who had not completed therapy with RCI had reduced odds of improvement in inflammation vs those who had completed a course of RCI treatment (OR=0.47; 95% CI, 0.27–0.83).[72]

In a subgroup analysis of 168 African Americans included in the Chopra et al 2019 chart review, 95% (160/168) experienced an improvement in current health status after treatment;[73] this result corroborates the result observed with the full cohort. Treatment with RCI was associated with a significant reduction in the proportion of patients taking glucocorticoids during treatment (59.5% at baseline vs 26.8% during treatment; $p<0.001$) and 3 months following treatment (26.8% during treatment vs 11.9% following treatment; $p<0.001$).[73] Patient safety was not quantified in the study. A retrospective 2-center chart review of 47 patients with refractory sarcoidosis who received RCI for ≥6 months found that, of the 29 who completed 3 months of treatment, 11 had improved disease, 16 had stable disease, and 2 had relapsed.[71] Of the 47 patients treated with RCI, those receiving treatment at study

entry for diabetes (n=23) or systemic hypertension (n=33) had no significant increase and no clinically significant decrease in their treatment medications in the first 6 months of RCI therapy.[71]

Economic Benefits

Currently, no study has examined the economic benefits of RCI for patients with symptomatic sarcoidosis.

Summary

Use of RCI has been shown to decrease many symptoms of sarcoidosis, and some patients who received RCI for sarcoidosis were able to decrease their use of any concomitant medication and decrease their daily dose of oral steroids by nearly half. Two expert panels list RCI as an option for patients with advanced disease and continuing disease activity despite standard treatment.

Proteinuria in Nephrotic Syndrome

NS is a constellation of renal and extrarenal manifestations that can be caused by a multitude of systemic diseases as well as by primary insults to the kidney. Of the primary renal causes, focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), minimal change disease (MCD), and immunoglobulin A neuropathy (IgAN) are the most common. RCI is indicated for inducing a diuresis or a remission of proteinuria in NS without uremia of the idiopathic type or that due to lupus erythematosus. Evidence for the benefits of RCI in NS is presented in Table S8.

Clinical Benefits

Clinical studies (randomized controlled studies, open-label studies), retrospective case series, and case reports have shown that RCI may be effective in achieving complete or partial remission of proteinuria in NS.[74–79] For example, in a combined prospective trial and retrospective review of 24 patients with proteinuria due to FSGS, 7 patients achieved remission with RCI.[74]

Similarly, a prospective open-label trial of RCI showed that 8 of 15 patients with various NS etiologies saw a reduction in proteinuria; this included 2 of 5 patients with resistant idiopathic MN, 2 of 5 patients with MCD or FSGS, and 4 of 5 patients with IgAN. No patient developed a significant infection during the study.[75]

Economic Benefits

In a claims database analysis conducted among US patients with a diagnosis of NS, all-cause HCRU and costs were evaluated in the 12 months before drug initiation with RCI or rituximab to characterize patients initiating therapy. Across groups, more pre-rituximab patients than pre-RCI patients had >3 inpatient stays and the average LOS was higher for pre-rituximab patients than pre-RCI patients in the commercial (MN + IgAN combined; 3.83 days vs 2.08 days), MN (6.24 days vs 1.6 days), and IgAN (3.78 days vs 2.78 days) subgroups.[80] Pre-rituximab patients had consistently greater inpatient, outpatient, and pharmacy costs than pre-RCI patients, leading to higher total all-cause health care costs.

Summary

Prospective studies and retrospective case series have shown the potential effectiveness of RCI for complete or partial remission of proteinuria in NS. The economic benefits of RCI in patients with NS have yet to be established.

Conclusions

Literature from clinical trials and real-world studies suggest that RCI is safe and effective for the treatment of inflammatory and progressive neurological, rheumatological, respiratory, ophthalmological, and other diseases, including for use as first-line therapy for IS and as a subsequent line of therapy during acute exacerbation and as maintenance therapy in other approved indications. Many of these are rare and serious illnesses, giving patients a much-needed treatment option that they would otherwise be lacking. RCI also represents an important treatment option for patients experiencing nonresponse or intolerance to traditional interventions, again giving clinicians an additional safe and efficacious tool by which to help improve clinical and related outcomes. Adverse effects generally mirror those seen

with corticosteroids, and overall, RCI appears to be well tolerated. RCI has also demonstrated economic benefits in numerous indications, including cost effectiveness in MS relapse, RA, and SLE and reduced HCRU and/or costs in IS, MS relapse, RA, SLE, DM/PM, and NS. Three US clinical trials of RCI for lupus nephritis (NCT02226341), scleritis (NCT03465111), and proliferative vitreoretinopathy (NCT03727776) are currently recruiting, with several more in active phase or being planned (eg, NCT02523092).

Ethics Approval

This article did not involve any studies on human participants and, therefore, it did not require informed consent or institutional review board approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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