

Cost-Effectiveness of Repository Corticotropin Injection for the Treatment of Acute Exacerbations in Multiple Sclerosis

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Background: Relapses are common among patients with multiple sclerosis (MS) despite treatment with disease-modifying therapies. Repository corticotropin injection (RCI, Acthar® Gel), plasmapheresis (PMP), and intravenous immunoglobulin (IVIg) are alternative therapies for MS relapse. There is a dearth of economic assessments of these therapies for the acute exacerbations of MS. This study estimated the cost-effectiveness of RCI compared to PMP or IVIg.

Methods: A Markov state-transition model compared outcomes (costs, relapses, remission, and utilities) with RCI versus PMP or IVIg for the acute exacerbations in MS. The model was developed from the United States (US) payer and societal perspectives over one to three years. Patients initiated on alternative therapies were evaluated in one-day increments for the first 30 days during treatment. The model assumes the natural history of MS after treatment in the first month, adjusting for the effect of treatment. Incremental cost-effectiveness ratios (ICERs) were estimated as cost per quality-adjusted life-year (QALY) gained. The uncertainty in model parameters was evaluated in probabilistic sensitivity analyses.

Results: In the base case, RCI has an ICER of USD 42,078 per QALY compared to PMP over one year from the payer perspective and is dominant over two and three years; RCI is dominant compared to PMP from the societal perspective over all three years. Compared to IVIg, RCI is a dominant strategy from both payer and societal perspectives over all three years. Probabilistic sensitivity analysis supports the base case findings, suggesting that RCI may be cost-effective versus PMP and IVIg for acute exacerbations in MS.

Conclusion: RCI is a cost-effective alternative treatment for MS relapses compared to PMP and IVIg from the US payer and societal perspectives.

Keywords: Acthar® Gel, cost-effectiveness analysis, acute exacerbation, multiple sclerosis, quality-adjusted life-year, repository corticotropin injection

Introduction

Multiple sclerosis (MS) is a chronic autoimmune and inflammatory disease of the central nervous system. MS is characterized by episodes of reversible relapses.¹ There is variability in the clinical course and severity of symptoms in MS, with the most common symptoms being bladder or bowel dysfunction, blurred vision, cognitive impairment, impaired balance, numbness and tingling, fatigue, vertigo, and weakness.^{2,3} It is estimated that approximately 400,000 adults in the United States (US) may have MS; however, the epidemiology of MS may be underestimated.⁴ Relapses are common among patients with MS despite treatment

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with disease-modifying therapies; with 55.7% of the patients having at least one relapse (based on annualized relapse rate).⁵ Studies have shown that about one-fifth of patients may experience more than two relapses per year.⁶ Continued relapses result in considerable functional impairment and have a negative impact on the patient's quality of life.⁷

Corticosteroids are recommended as first-line agents for managing MS relapses.² Patients who fail corticosteroid therapy may be susceptible to worsening disease. These patients may require hospitalization and/or rehabilitation for disease management. Further, for some patients, high-dose corticosteroids may be contraindicated. Following corticosteroid failure, these patients transition to alternative therapies to alleviate acute exacerbations. Alternative therapies to address exacerbations among patients who fail oral corticosteroids comprise repository corticotropin injection (RCI, Acthar® Gel), plasmapheresis (PMP), and intravenous immunoglobulin (IVIg).⁸ The American Academy of Neurology recommends PMP as a second-line treatment for steroid-resistant exacerbations in relapsing forms of MS.^{9,10} Although PMP is a conventional treatment approach, the potential effectiveness of plasma exchange in the treatment of MS remains unclear.¹¹ IVIg is a pooled preparation of normal immunoglobulin G derived from the plasma of healthy donors. IVIg is occasionally used as an off-label treatment for patients non-responsive to corticosteroids.^{12,13} Limited clinical trial experience, small sample size, heterogeneity among study subjects, and variability in the dose provide little evidence to support the efficacy of IVIg in the treatment of relapses.¹⁴

RCI is a naturally sourced complex mixture of adrenocorticotrophic hormone analogs and other pituitary peptides.¹⁵ RCI is the only non-corticosteroid therapy indicated for the treatment of acute exacerbations of MS in adults by the US Food and Drug Administration.¹⁵ The unique mechanism of action of RCI is distinct from glucocorticoids. Therefore, RCI may have a different adverse event profile than glucocorticoids, ensuing in the removal of language referring to the similarity of adverse events of RCI and glucocorticoids.¹⁵ The efficacy and safety of RCI in acute exacerbations in MS has been demonstrated in controlled clinical trials.^{7,16} Further, clinically meaningful improvements in MS Impact Scale 29 item version 1 (MSIS-29v1) physical subscale were observed in a prospective observational study of patients with treatment-refractory MS on RCI.¹⁷ Statistically significant

improvements in clinician-rated scales (Expanded Disability Status Scale [EDSS] and Clinical Global Impression of Improvement [CGI-I]) were also observed.¹⁷ A retrospective claims analysis comparing RCI and alternative therapies supported the effectiveness of RCI in reducing relapses in MS.^{8,18} Further, a recent literature review corroborates the efficacy of RCI in MS.¹⁶ Initial economic analyses indicated that RCI was cost-saving compared to PMP or IVIg in resolving MS relapses from a payer perspective.^{19,20} Considering the societal burden of MS relapses,²¹ it is important to evaluate these treatments considering this perspective to optimize patient care. Further, there is a dearth of economic assessments on the cost-effectiveness of RCI, PMP, and IVIg for the acute exacerbations in MS. Cost-effectiveness analyses serve as a foundation to integrate clinical, real-world, economic, and humanistic evidence to support decision-making. This study estimated the cost-effectiveness of RCI for the treatment of acute exacerbations in MS compared to alternative therapies (PMP and IVIg) from the US payer and societal perspectives.

Methods

The analysis was conducted consistent with the International Society for Pharmacoeconomics and Outcomes Research Good Practice Guidelines for cost-effectiveness analysis²² and recommendations on cost-effectiveness in health and medicine.²³

Model Overview

The model is a probabilistic state-transition model that evaluates the economic and quality-of-life outcomes of treating patients with MS. The model comprises of two states—relapse/exacerbation and remission/response—mirroring those in the life of a patient with MS (Figure 1). The model included only those patients with active relapses. Each health state is further based on the EDSS state (EDSS 0–8+) in one-point increments. The EDSS classification is widely used in clinical trials to define MS progression.²⁴ Patients are allowed to move between exacerbation or response/remission state within an EDSS state, but cannot move among EDSS states. The transition of patients in the model is consistent with the treatment recommendations;²⁵ RCI, PMP, and IVIg are used for the treatment of acute exacerbations in MS and not for slowing disease progression, measured using EDSS. Therefore, we did not consider the movement of patients across EDSS states. EDSS states were included to

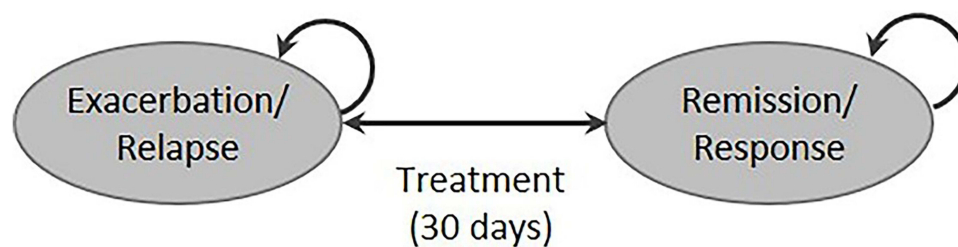


Figure 1 Schematic of the state-transition model. Treatments include RCI, PMP, IVIg was given over 30 days. The administration is consistent with current clinical practices and recommendations.

Abbreviations: IVIg, intravenous immunoglobulin; PMP, plasmapheresis; RCI, repository corticotropin injection.

account for variability in clinical and pharmacoeconomic outcomes among patients with varying disease severity. The model was developed from the US payer and societal perspectives over three years in Microsoft® Excel 2019 (Redmond, Washington, US).

Initially, all patients start in the exacerbation state across nine EDSS states. A natural history matrix is applied to the probability of treatment success with RCI, PMP, or IVIg to derive a treatment-specific transition from exacerbation to remission in the first 30 days (on-treatment). The 30-day criterion was selected based on a published claims-based methodology.²⁶ This methodology comprises an inpatient or outpatient claim with a diagnosis of MS followed by receipt of a relapse treatment or procedure (RCI, PMP, or IVIg).²⁷ Patients accrue in the exacerbation or response state for 30 days in daily increments. Following the on-treatment period, the natural history of relapsing-remitting MS is used to estimate the number of patients in each health state over three years with a cycle length of one month. Treatments are administered consistent with the current recommendations and clinical practices.^{15,27}

Model Inputs

Clinical Probabilities

The EDSS provides a method to quantify MS severity by monitoring the level of disability in patients over time. Higher EDSS score indicates an increasing level of disease severity and worsening health outcomes.^{28,29} To simplify the assessment of outcomes and mitigate uncertainty in the model, the model categorized disease severity based on EDSS states; patients with EDSS ≤ 4.0 were considered having a mild/moderate disease, while those with EDSS >4.0 were considered having severe disease consistent with current scaling.³⁰ Baseline patient distribution by EDSS state and relapse severity were derived from the MS Relapse Registry, titled “Observational Registry of Acthar Gel for Participants with Multiple Sclerosis Relapse,” funded by Mallinckrodt

Pharmaceuticals (N = 125; Table 1).^{17,31} The study was conducted to monitor the course of MS and to document relapses and the recovery process, in a group of MS patients treated with RCI.

During the on-treatment period, the treatment-related probability of relapse resolution in the first 30 days was used. The probabilities were sourced from a retrospective study utilizing administrative claims data between January 01, 2008 and June 30, 2015. The monthly probabilities were converted to daily probabilities as appropriate. The study evaluated the treatment effectiveness of RCI, PMP, and IVIg in patients 18–89 years of age who experienced an MS relapse. The proportion of patients achieving relapse resolution with RCI, PMP, and IVIg was 96.9%, 50.7%, and 43.9%, respectively.⁸ The response state was considered the absorbing state during the on-treatment period; it was assumed that patients achieving a response remain in that state for the duration of the on-treatment period.

Table 1 Baseline Patient Distributions by EDSS State and Relapse Severity

| Parameter | Initial Distribution ⁴⁶ (N=125) | Mild/ Moderate Relapse ^{28,29} | Severe Relapse ^{28,29} |
|-----------|---|---|------------------------------------|
| EDSS 0 | 1.65% | 98.3% | 1.7% |
| EDSS 1 | 9.09% | 95.6% | 4.4% |
| EDSS 2 | 20.66% | 89.9% | 10.1% |
| EDSS 3 | 23.97% | 69.5% | 30.5% |
| EDSS 4 | 10.74% | 40.0% | 60.0% |
| EDSS 5 | 3.31% | 13.4% | 86.6% |
| EDSS 6 | 23.14% | 4.4% | 95.6% |
| EDSS 7 | 6.61% | 1.6% | 98.4% |
| EDSS 8+ | 0.83% | 0.0% | 100.0% |

Notes: Patients with EDSS of 4.0 have a significant disability but are self-sufficient and up and about some 12 hours a day, are able to walk without aid, or rest for 500 meters; those with EDSS of 4.5 have a significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance, are able to walk without aid, or rest for 300 meters.³⁰

Abbreviation: EDSS, Expanded Disability Status Scale.

During the off-treatment period, the probability of relapse was estimated as a function of baseline treatment and EDSS state (Table 2). The probability of response was derived from a retrospective study using the mean number of relapse episodes in the 12-month follow-up period after administration of RCI or PMP/IVIg.⁸

The transition probability of exacerbation to response/remission state during the off-treatment period was similarly based on baseline treatment (Table 2) and EDSS state and was derived as follows:

$$P(\text{Treatment} | \text{Response}) = \frac{P(\text{Treatment} \cap \text{Response})}{P(\text{Response})}$$

Adverse Events

For each treatment, only serious adverse events (SAEs) were applied in the model since SAEs account for the greatest economic impact on the healthcare system and patients. The probabilities of SAEs for RCI were sourced from the MS Relapse Registry and the published literature for PMP and IVIg. The SAE rates are presented in Table 3.

Table 2 Adjusted Monthly Transition Probabilities During the Off-Treatment Period

| EDSS State | RCI | PMP or IVIg |
|--------------------------|--------|-------------|
| Response to exacerbation | | |
| EDSS 0 | 0.0685 | 0.0974 |
| EDSS 1 | 0.0723 | 0.1027 |
| EDSS 2 | 0.0632 | 0.0900 |
| EDSS 3 | 0.0703 | 0.1000 |
| EDSS 4 | 0.0685 | 0.0974 |
| EDSS 5 | 0.0498 | 0.0711 |
| EDSS 6 | 0.0378 | 0.0542 |
| EDSS 7 | 0.0400 | 0.0573 |
| EDSS 8+ | 0.0400 | 0.0573 |
| Exacerbation to response | | |
| EDSS 0 | 0.3016 | 0.0068 |
| EDSS 1 | 0.3010 | 0.0067 |
| EDSS 2 | 0.3025 | 0.0068 |
| EDSS 3 | 0.3013 | 0.0068 |
| EDSS 4 | 0.3016 | 0.0068 |
| EDSS 5 | 0.3047 | 0.0069 |
| EDSS 6 | 0.3066 | 0.0069 |
| EDSS 7 | 0.3063 | 0.0069 |
| EDSS 8+ | 0.3063 | 0.0069 |

Abbreviations: EDSS, Expanded Disability Status Scale; IVIg, intravenous immunoglobulin; PMP, plasmapheresis; RCI, repository corticotropin injection.

Costs

The model included treatment costs (drug and administration costs), cost of adverse events, direct medical, direct non-medical, and indirect cost of relapse, and the base cost of relapse by EDSS score (direct and indirect costs). The model assumed that all patients incur the cost of conventional therapy after the first cycle (off-treatment period).

Wholesale acquisition costs were used for the cost of drug acquisition. The administration, dose strength, and dosing were obtained from the real-world use and prescribing information.^{27,32} Administration costs were applied to PMP and IVIg but not RCI since RCI is a self-administered treatment. Treatment with PMP assumed an average dose of 40 mL/kg (patient weight of 79.1 kg)³³ and six sessions;²⁷ treatment with IVIg assumed an average dose of 400 mg/kg and five sessions followed by maintenance therapy every four weeks.^{27,34} Drug acquisition and administration costs are presented in Table 4. Direct and indirect costs of exacerbation/relapse and remission/response were categorized by disease severity (mild/moderate and severe MS). Productivity loss and absenteeism costs were estimated using the human capital approach.³⁵ Finally, the cost of relapse of the baseline MS by EDSS state was added to the overall costs.³⁶ All costs were discounted at 3.0% annually and reported in 2021 United States Dollars (USD).

Table 3 SAEs for Treatments

| Adverse Event | Value | Source |
|-------------------------------|--------|-----------------------------|
| RCI | | |
| Asthenia | 1.60% | Kaplan 2020 ⁴⁶ |
| Urinary tract infection | 1.60% | Kaplan 2020 ⁴⁶ |
| PMP | | |
| Bleeding | 4.90% | Heatwole 2011 ²⁷ |
| Infection | 4.90% | Heatwole 2011 ²⁷ |
| Catheter occlusion | 2.40% | Heatwole 2011 ²⁷ |
| Deep vein thrombosis | 2.40% | Heatwole 2011 ²⁷ |
| IVIg | | |
| Fever | 14.80% | Heatwole 2011 ²⁷ |
| Increased creatinine | 14.80% | Heatwole 2011 ²⁷ |
| Abnormal liver function tests | 8.00% | Heatwole 2011 ²⁷ |
| Stroke | 0.60% | Heatwole 2011 ²⁷ |

Abbreviations: IVIg, intravenous immunoglobulin; PMP, plasmapheresis; SAE, serious adverse event; RCI, repository corticotropin injection.

Table 4 Economic Input Parameters

| Cost Parameter | Value | | Source |
|---|--------------------------------|-----------|---|
| Treatment costs | | | |
| RCI ^a | \$39,864 per vial ^b | | Red Book ⁴⁷ |
| PMP Albuminar [®] 5% (40 mL/kg; per session) ^c | \$180.00 ^b | | Red Book; ⁴⁷ Navarro-Martinez 2020 ⁴⁸ |
| Administration cost | | | |
| Central venous catheter (including supplies) | \$1010.49 | | Winters et al ⁴⁹ |
| Tubing set and other supplies | \$282.74 | | Winters et al ⁴⁹ |
| Fibrinogen lab test | \$101.90 | | CPT 85384 ⁵⁰ |
| Plasma exchange equipment amortization | \$353.90 | | Winters et al ⁴⁹ |
| Service contract amortization | \$148.05 | | Winters et al ⁴⁹ |
| Professional costs (3 hours) | \$1037.52 | | CPT 99214 ⁵⁰ |
| Facility cost ^d | \$1575.44 | | CPT 99236 ⁵⁰ |
| IVIg Gamunex-C [®] (400 mg/kg; per session) ^e | \$130.12 ^b | | Red Book ⁴⁷ Katz 2006 ⁵¹ |
| Administration cost | | | |
| IVIg infusion supplies | \$202.90 | | CPT 96365, 96366 ⁵⁰ |
| Professional costs (2 hours) | \$691.68 | | CPT 99214 ⁵⁰ |
| Facility cost ^d | \$1575.44 | | CPT 99236 ⁵⁰ |
| Adverse events | | | |
| Asthenia | \$2020 | | Strand 2020 ⁵² |
| Urinary tract infection | \$1412 | | Hagiwara 2013 ⁵³ |
| Bleeding | \$581 | | Heatwole 2011 ²⁷ |
| Catheter occlusion | \$2264 | | Heatwole 2011 ²⁷ |
| Deep vein thrombosis | \$5355 | | Heatwole 2011 ²⁷ |
| Infection | \$2032 | | Heatwole 2011 ²⁷ |
| Fever | \$2032 | | Heatwole 2011 ²⁷ |
| Increased creatinine | \$302 | | Heatwole 2011 ²⁷ |
| Abnormal liver function tests | \$293 | | Heatwole 2011 ²⁷ |
| Stroke | \$77,062 | | Heatwole 2011 ²⁷ |
| Direct medical costs | Mild/Moderate | Severe | |
| Ambulatory care | \$72.45 | \$17.39 | O'Brien 2003 ⁵⁴ |
| Inpatient | \$485.61 | \$1962.89 | O'Brien 2003 ⁵⁴ |
| Physician visit | \$25.93 | \$25.93 | O'Brien 2003 ⁵⁴ |
| Home health services | \$120.79 | \$311.59 | O'Brien 2003 ⁵⁴ |
| Direct non-medical costs | Mild/Moderate | Severe | |
| Community service | \$96.50 | \$96.96 | Oleen-Burkey 2012 ²¹ |
| Alterations and adaptations | \$372.65 | \$347.95 | Oleen-Burkey 2012 ²¹ |
| Travel/Meals | \$40.32 | \$180.17 | O'Connell 2014 ⁵⁵ |
| Indirect costs | Mild/Moderate | Severe | |
| Medically related absenteeism | \$165.01 | \$241.31 | Parisé 2013 ⁵⁶ |
| Reduced productivity at work (presenteeism) | \$349.69 | \$496.29 | Oleen-Burkey 2012 ²¹ |
| Disability | \$187.43 | \$513.96 | Parisé 2013 ⁵⁶ |
| Informal care | \$304.80 | \$564.72 | Oleen-Burkey 2012 ²¹ |
| Family's loss of earnings | \$161.85 | \$239.89 | Parisé 2013 ⁵⁶ |

Notes: ^a2.33 vials are assumed per relapse. ^bWholesale acquisition costs. ^cThe model assumes six sessions²⁷ and an average weight of 79 kg.³³ Based on a dose of 40 mL/kg, the cost of 5% albumin per session is \$1260 or \$7560 for six sessions. Including the administration costs, the total cost of treatment per session is \$5770 (or \$34,620 for six sessions). ^dAssumes outpatient facility costs for administration of PMP and IVlg. ^eThe model assumes five doses²⁷ and an average weight of 79 kg.³³ Based on a dose of 400 mg/kg, the cost of IVlg is \$4164 per session or \$20,820 for five sessions. Including the administration costs, the cost of treatment per session is \$6634 (or \$33,168 for five sessions). Note that the model also includes maintenance treatment for IVlg every 4 weeks, so the overall cost of treatment with IVlg is considerably larger.

Abbreviations: CPT, current procedural terminology; IVlg, intravenous immunoglobulin; PMP, plasmapheresis; RCI, repository corticotropin injection.

Health Utilities

The health utility of MS during exacerbation/relapse and remission/response by EDSS state was sourced from the published literature (Table 5).²⁸ The utility decrement due to relapse was based on the disease severity—0.091 and 0.302 for mild/moderate and severe MS relapse, respectively.²¹ All health utilities were discounted at 3.0% annually.

Sensitivity Analyses

Probabilistic sensitivity analyses (PSA) were performed to account for the uncertainty around model parameters and to test the robustness of the model using appropriate distributions.

Results

Base Case Analysis

Considering the payer perspective over one year, RCI results 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 per QALY compared to PMP (Table 6). However, RCI is a dominant treatment strategy from the payer perspective over two and three years with an average cost savings of \$6827 to \$18,551 and an average QALY gain of 0.241 to 0.368 compared to PMP. RCI is a dominant treatment strategy compared to IVIg from the payer perspective with an average cost savings of \$79,867, \$177,939, and \$275,954 over year 1, year 2, and year 3, respectively. Considering the societal perspective, RCI is a dominant treatment

Table 5 Health Utilities of Remission/Response and Exacerbation/Relapse for Baseline MS

| EDSS State | Remission/Response | Mild/Moderate Relapse | Severe Relapse |
|------------|--------------------|-----------------------|----------------|
| EDSS 0 | 0.8752 | 0.7842 | 0.5732 |
| EDSS 1 | 0.8342 | 0.7432 | 0.5322 |
| EDSS 2 | 0.7802 | 0.6892 | 0.4782 |
| EDSS 3 | 0.6946 | 0.6036 | 0.3926 |
| EDSS 4 | 0.6253 | 0.5343 | 0.3233 |
| EDSS 5 | 0.5442 | 0.4532 | 0.2422 |
| EDSS 6 | 0.4555 | 0.3645 | 0.1535 |
| EDSS 7 | 0.3437 | 0.2527 | 0.0417 |
| EDSS 8+ | 0.0023 | -0.0887 | -0.2997 |

Abbreviation: EDSS, Expanded Disability Status Scale.

Table 6 Cost-Effectiveness of RCI Compared to PMP or IVIg

| Treatment | Incremental Costs | Incremental QALYs | ICER |
|---------------------|-------------------|-------------------|----------|
| Payer at 1 year | | | |
| RCI vs PMP | \$4839 | 0.115 | \$42,078 |
| RCI vs IVIg | (\$79,867) | 0.120 | Dominant |
| Societal at 1 year | | | |
| RCI vs PMP | (\$10,508) | 0.115 | Dominant |
| RCI vs IVIg | (\$95,923) | 0.120 | Dominant |
| Payer at 2 years | | | |
| RCI vs PMP | (\$6827) | 0.241 | Dominant |
| RCI vs IVIg | (\$177,939) | 0.248 | Dominant |
| Societal at 2 years | | | |
| RCI vs PMP | (\$39,184) | 0.241 | Dominant |
| RCI vs IVIg | (\$211,229) | 0.248 | Dominant |
| Payer at 3 years | | | |
| RCI vs PMP | (\$18,551) | 0.368 | Dominant |
| RCI vs IVIg | (\$275,954) | 0.376 | Dominant |
| Societal at 3 years | | | |
| RCI vs PMP | (\$67,972) | 0.368 | Dominant |
| RCI vs IVIg | (\$326,372) | 0.376 | Dominant |

Notes: RCI is the reference category; positive cost represents the cost incurred with RCI; positive QALYs represent QALYs gained with RCI.

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PMP, plasmapheresis; QALY, quality-adjusted life-year; RCI, repository corticotropin injection.

strategy over all three years compared to both PMP and IVIg. A detailed breakdown of costs is provided in Table 7.

Sensitivity Analyses

The PSA randomly sampled the selected distributions during each of the 1,000 iterations (Figure 2). RCI was cost-effective compared to PMP or IVIg, consistent with the base case findings. RCI was cost-effective at a willingness-to-pay (WTP) threshold of \$100,000. Rebates and drug price discounts may further enhance the cost-effectiveness of RCI.

Discussion

Relapses are common among patients with MS, which may result in a high economic burden on the patients and adversely impact the health-related quality of life and functional ability of the patients.³⁷ Corticosteroids are recommended as the first-line agents for managing MS relapses.² Patients who fail corticosteroid therapy may be at a high risk of worsening disease, requiring hospitalization and/or rehabilitation for disease

Table 7 Breakdown of Costs

| Parameter | RCI | PMP | IVIg |
|-------------------|------------------|------------------|------------------|
| YEAR 1 | | | |
| Treatment cost | \$55,494 | \$38,427 | \$119,897 |
| AE cost | \$394 | \$2071 | \$4811 |
| Direct cost | \$13,924 | \$24,475 | \$24,971 |
| Indirect cost | \$32,002 | \$47,349 | \$48,058 |
| Total cost | \$101,814 | \$112,322 | \$197,737 |
| QALYs | 0.608 | 0.493 | 0.488 |
| YEAR 2 | | | |
| Treatment cost | \$55,494 | \$38,427 | \$206,137 |
| AE cost | \$394 | \$2071 | \$4811 |
| Direct cost | \$27,496 | \$49,713 | \$50,375 |
| Indirect cost | \$62,843 | \$95,200 | \$96,133 |
| Total cost | \$146,227 | \$185,411 | \$357,456 |
| QALYs | 1.175 | 0.934 | 0.927 |
| YEAR 3 | | | |
| Treatment cost | \$55,494 | \$38,427 | \$292,377 |
| AE cost | \$394 | \$2071 | \$4811 |
| Direct cost | \$40,268 | \$74,209 | \$74,922 |
| Indirect cost | \$91,864 | \$141,285 | \$142,282 |
| Total cost | \$188,020 | \$255,992 | \$514,392 |
| QALYs | 1.709 | 1.341 | 1.333 |

Abbreviations: AE, adverse event; IVIg, intravenous immunoglobulin; PMP, plasmapheresis; QALY, quality-adjusted life-year; RCI, repository corticotropin injection.

management. These patients may be eligible to receive alternative therapy; however, there is no definitive guidance in the US for the use of these therapies. RCI is the only non-corticosteroid therapy indicated for the treatment of acute exacerbations of MS in adults approved by the US Food and Drug Administration.¹⁵ PMP is recommended by the American Academy of Neurology,^{9,10} whereas IVIg is an off-label treatment for MS relapses, with limited supporting evidence.^{12,13} There is a lack of data regarding the costs and benefits of RCI in clinical practice in the US. This is the first study to evaluate the cost-effectiveness of RCI versus PMP and IVIg. Cost-effectiveness analyses are important tools to compare different healthcare interventions and aid in decision-making.

Our analyses suggest that RCI is a cost-effective treatment strategy compared to PMP and IVIg. Considering the payer perspective over one year, the use of RCI is cost-effective (ICER: \$42,078 per QALY) compared to PMP at the commonly used WTP threshold of \$100,000 to \$150,000 per QALY. RCI is dominant compared to

PMP over two and three years. The findings suggest that the initial cost of RCI is offset by long-term cost savings and gain in QALYs. RCI is a dominant treatment strategy over IVIg due to the high cost of IVIg treatment and limited effectiveness in treating MS relapses. These results are consistent with previous economic evaluations where RCI was cost-saving compared to PMP or IVIg.^{19,20} However, these prior economic evaluations only focused on the direct cost of treatment and did not consider the clinical characteristics of patients with MS relapse.

RCI is an effective and well-tolerated treatment that expedites the resolution of acute exacerbations in MS.^{7,8,16,18} Further, RCI use is convenient for patients as it can be self-administered.¹⁵ In contrast, both PMP and IVIg are administered in the hospital setting for acutely limited patients and are more intensive treatments. Collectively, this clinical and economic evidence demonstrates the health economic value of RCI over PMP and IVIg. Treatment costs are central to concerns of access and affordability; however, it is important to consider the clinical, economic, and humanistic value of treatments. Value is defined as the potential benefits of interventions for their costs³⁸ and is measured using cost-effectiveness metrics. Interventions that offer substantial benefits are recognized as those with high “Care Value” (ICER ranging from \$100,000 to \$150,000 per QALY).^{39,40} This ICER threshold of 3 times nation’s per capita income is based on the recommendations of the World Health Organization’s Choosing Interventions that are Cost Effective (WHO-CHOICE).⁴¹

Despite recent advances in treatment, patients with MS experience functional disability, which affects their daily activities and work productivity.^{21,42} These patients may require ongoing care and support that adds to the overall economic and patient burden.^{21,43} In a comprehensive cost-effectiveness analysis, costs should include healthcare costs downstream of the intervention and indirect costs due to productivity loss and caregiver burden, in addition to the direct costs of the intervention.⁴⁴ The lost productivity is notable for patients with MS, who have to often leave the workforce as a result of their disability.⁴⁵ The current analysis includes costs accrued due to increased disability, caregiver costs, and cost due to lost productivity of patients in addition to medical and pharmacy costs. The findings indicate that RCI is a dominant treatment strategy compared to both PMP and IVIg over all three years from the societal perspective.

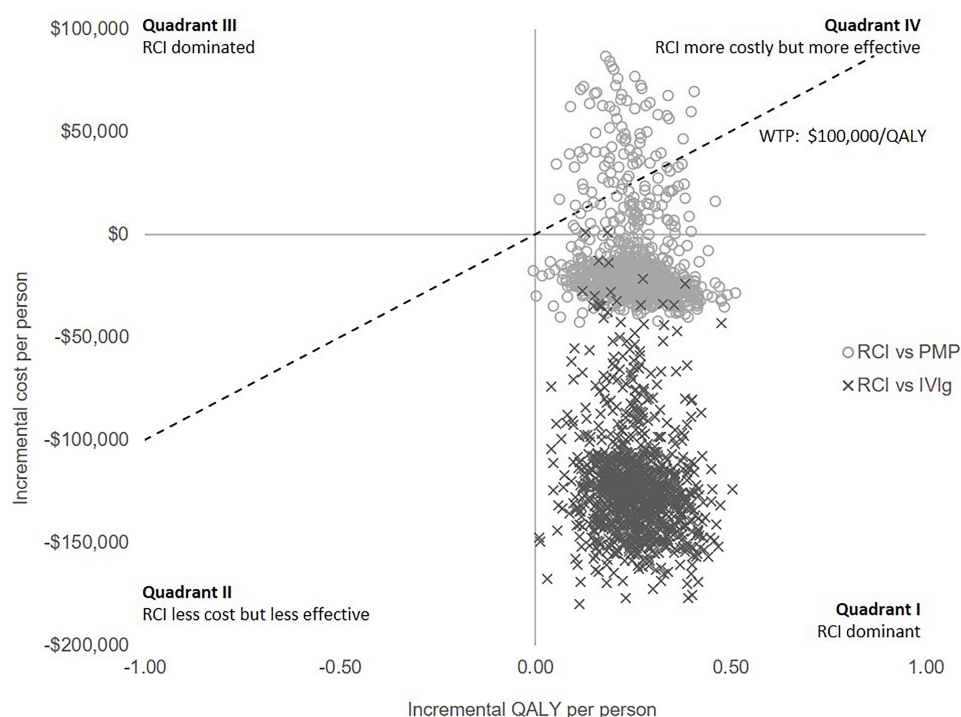


Figure 2 Results of the probabilistic sensitivity analyses for the cost-effectiveness of RCI compared to PMP or IVIg from a US payer perspective over two years.

Abbreviations: IVIg, intravenous immunoglobulin; PMP, plasmapheresis; RCI, repository corticotropin injection; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

Besides the model assumptions, this analysis has some limitations. First, the cost of additional treatment for patients who experience relapse was not included, which may enhance the cost-effectiveness of RCI. Second, the transition of patients between EDSS states was not considered since the treatments are prescribed for acute exacerbations in MS and due to the short duration of treatment. Finally, while wholesale acquisition cost is appropriate for health economic models, price negotiations and other factors (eg, discounts, rebates, and value-based arrangements) may alter the actual cost to the US payers. Some limitations are inherent to the model. The cost and utility estimates were obtained from various literature sources, which may add uncertainty and heterogeneity to the model. Preferably, information from large, high-quality, head-to-head trials should be used to inform comparative effectiveness assessments. The PSA was conducted to account for uncertainty in the estimates and the findings were consistent with the base case analyses.

Conclusions

RCI is a cost-effective alternative treatment for MS relapses compared to PMP and IVIg from the US payer

and societal perspectives. Further clinical and economic analyses should assess the long-term clinical- and cost-effectiveness of RCI, PMP, and IVIg for acute exacerbations in MS.

Data Sharing Statement

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Compliance with Ethics Guidelines

This study does not involve any human participants, human data, and/or human material. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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Disclosure

GJW and JN are employees at Mallinckrodt Pharmaceuticals. JB and MP were paid consultants at Mallinckrodt Pharmaceuticals for the duration of the project. IC was a research collaborator for the duration of the study. SFH is a research collaborator and has received speaker honoraria, consulting agreements, and grant/research financial support from AbbVie, Acorda, Actelion, Adamas, Alkermes, Avanir, Bayer, Biogen Idec, Bristol Meyers Squibb, EMD Serono, Janssen-Actelion, Novartis, Osmotica, Mallinckrodt, Roche, Sanofi, Synthon, and Teva. All authors declare that they have no other conflicts of interest.

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