

Corticosteroid use and adherence in patients treated with Acthar® Gel for advanced sarcoidosis

Kyle Hayes¹, John Niewoehner¹, J Bradford Rice², Nathaniel Downes², Ella Hagopian², Izzy Ma², George J Wan¹

1: Mallinckrodt Pharmaceuticals, Bridgewater, NJ; 2: Analysis Group Inc, Boston, MA



Study background

Acthar® Gel (Repository Corticotropin Injection, RCI) for the Treatment of Symptomatic Sarcoidosis

Background

- Sarcoidosis is a multisystem, inflammatory disease characterized by formation of granulomas in any organ systems, most commonly the lungs
- The global incidence and prevalence of sarcoidosis is between 7.6-8.4 and 59.0-60.1 per 100,000, respectively¹
- First line treatment for symptomatic sarcoidosis is corticosteroids (CS), per treatment guidelines and current clinical practice
- Sarcoidosis patients treated with high dose, long term CS (>500 mg/year) have been shown to have significantly lower health-related quality of life (HRQoL) for the domains of fatigue, daily activities, and general satisfaction compared to <500 mg/year, even when accounting for disease severity²
- Higher medication adherence is associated with better HRQoL as measured by the St. George's Respiratory Questionnaire (SGRQ) and the King's Sarcoidosis Health Questionnaire (KSQ)³
- Acthar Gel (RCI) is indicated for the treatment of symptomatic sarcoidosis⁴ and is referenced in the European Respiratory Society (ERS) treatment guidelines among anti-inflammatory treatments for pulmonary sarcoidosis when other therapies are ineffective or not tolerated⁵
- The ERS guidelines list RCI, Rituximab, and Janus Kinase inhibitors (JAKi) as fourth line options in pulmonary sarcoidosis for patients who do not respond to corticosteroids or antimetabolites
- RCI is included in the US Sarcoidosis Delphi Expert Panel Consensus Statement recommendations for treatment of sarcoidosis⁶
- Due to the high steroid burden in treatment of symptomatic sarcoidosis, other steroid sparing alternatives are needed

Study Objectives

- Demonstrate improvement in CS burden after treatment with RCI and benefits of higher adherence to RCI in CS reduction in patients with symptomatic sarcoidosis

Study design

- Study Type:** This was a retrospective, longitudinal case-control study of administrative claims data (Symphony Health IDV, 2016-2021) comparing real-world treatment patterns and adherence to RCI for sarcoidosis
- Inclusion Criteria:** Confirmed diagnosis (defined as ≥2 medical claims) for sarcoidosis (ICD-10-CM of D86.x) and either a claim for RCI or comparable line treatment of Rituximab or Janus kinase inhibitors (JAKi), per ERS treatment guidelines. Patients were ≥18 years of age and had at least 12 months of continuous eligibility prior to and following the index date (date of first claim for a study treatment)
- RCI vs. Fourth Line:** The full RCI cohort was compared to the fourth line cohort (Rituximab and JAKi) for changes in GC use and treatment patterns
- RCI Above Average vs. Below Average Adherence Cohorts:** Patients who initiated therapy with RCI were grouped into adherence cohorts using the mean proportion of days covered (PDC) for all RCI patients in their follow-up period. Patients were split into "Above Average" with higher PDC than the RCI cohort mean value and Below Average for those below the mean PDC
- Comparisons between cohorts are based on mean change from baseline

Table 1: Baseline demographics and clinical characteristics

	RCI vs. Fourth Line		RCI Adherence Sample		P-value ⁴	
	All RCI	Fourth line ²	Above average ³	Below average ³		
	(N = 735)	(N = 626)	(N = 421)	(N = 314)		
Demographics⁵						
Age at index date (years)	54.71 ± 11.12	57.72 ± 12.39	<0.001	55.35 ± 11.18	53.85 ± 10.99	0.070
Gender (female), N (%)	498 (67.8%)	453 (72.4%)	0.066	284 (67.5%)	214 (68.2%)	0.842
Race/ethnicity, N (%)						
Asian	6 (0.8%)	3 (0.5%)	0.444	2 (0.5%)	4 (1.3%)	0.234
Black	228 (31.0%)	116 (18.5%)	<0.001	134 (31.8%)	94 (29.9%)	0.583
Hispanic	38 (5.2%)	40 (6.4%)	0.335	14 (3.3%)	24 (7.6%)	0.009
White	299 (40.7%)	342 (54.6%)	<0.001	172 (40.9%)	127 (40.4%)	0.911
Other	4 (0.5%)	6 (1.0%)	0.373	3 (0.7%)	1 (0.3%)	0.473
Unknown/Unspecified	160 (21.8%)	119 (19.0%)	0.209	96 (22.8%)	64 (20.4%)	0.432
Region, N (%)						
Midwest	157 (21.4%)	163 (26.0%)	0.043	90 (21.4%)	67 (21.3%)	0.990
Northeast	138 (18.8%)	148 (23.6%)	0.028	75 (17.8%)	63 (20.1%)	0.440
South	402 (54.7%)	247 (39.5%)	<0.001	236 (56.1%)	166 (52.9%)	0.390
West	38 (5.2%)	68 (10.9%)	<0.001	20 (4.8%)	18 (5.7%)	0.552
Insurance plan type at index date, N (%)						
Commercial	21 (2.9%)	307 (49.0%)	<0.001	11 (2.6%)	10 (3.2%)	0.645
Medicaid	69 (9.4%)	20 (3.2%)	<0.001	39 (9.3%)	30 (9.6%)	0.894
Medicare	241 (32.8%)	94 (15.0%)	<0.001	158 (37.5%)	83 (26.4%)	0.002
Pharmacy Benefit Management	81 (11.0%)	0 (0.0%)	<0.001	45 (10.7%)	36 (11.5%)	0.740
Unknown/Unspecified Plan	323 (43.9%)	0 (0.0%)	<0.001	168 (39.9%)	155 (49.4%)	0.012
Clinical Characteristics						
Charlson Comorbidity Index (CCI) ⁶ , Mean ± SD	1.31 ± 1.59	2.31 ± 1.89	<0.001	1.22 ± 1.55	1.44 ± 1.65	0.064
Quality of life metrics, N (%)						
Comorbid conditions						
Cardiovascular/circulatory	424 (57.7%)	416 (66.5%)	<0.001	242 (57.5%)	182 (58.0%)	0.896
Mental health	141 (19.2%)	170 (27.2%)	<0.001	72 (17.1%)	69 (22.0%)	0.097
Musculoskeletal	44 (6.0%)	53 (8.5%)	0.076	23 (5.5%)	21 (6.7%)	0.489
Respiratory	454 (61.8%)	355 (56.7%)	0.058	256 (60.8%)	198 (63.1%)	0.535
Other	360 (49.0%)	341 (54.5%)	0.043	198 (47.0%)	162 (51.6%)	0.221
Quality of care metrics, N (%)						
Blood testing	359 (48.8%)	484 (77.3%)	<0.001	197 (46.8%)	162 (51.6%)	0.198
Chest x-ray	46 (6.3%)	0 (0.0%)	<0.001	27 (6.4%)	19 (6.1%)	0.815
Lung function testing	273 (37.1%)	192 (30.7%)	0.012	138 (32.8%)	135 (43.0%)	0.005
Use of oxygen	64 (8.7%)	35 (5.6%)	0.027	37 (8.8%)	27 (8.6%)	0.928

Abbreviations: AIDS, autoimmune deficiency syndrome; CCI, Charlson Comorbidity Index; CS, corticosteroid; DMARD, disease-modifying anti-rheumatic drug; SD, standard deviation
 Notes:
 [1] Index date was defined as the first observed claim for Acthar following any diagnosis of sarcoidosis.
 [2] Fourth line therapies included oral JAK inhibitors and rituximab outlined in the European Respiratory Society treatment guidelines for sarcoidosis in Baughman et al. See Baughman, RP, et al. ERS clinical practice guidelines on treatment of sarcoidosis. *European Respiratory Journal*. 2021; 57(12):2004079.
 [3] Patients were classified as adherent if they had a calculated proportion of days covered (PDC) of Acthar in the 1-year follow-up period greater than the mean PDC for Acthar among the overall sample in that period.
 [4] Statistical testing was conducted using chi-square tests for categorical variables and t-tests for continuous variables.
 [5] Evaluated on the index date.
 [6] The Quan-Charlson Comorbidity Index (CCI), a composite measure of the patient's health status, was calculated based on the 17 conditions and respective weights set forth by Quan et al. See Quan, H, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005; 43(11): p. 1130-1139.

Baseline demographics and clinical characteristics

- RCI vs. Fourth Line:** At baseline, the RCI cohort was significantly younger (55 years vs. 58 years, p<0.001), had more black/African Americans (31.0% vs. 18.5%, p<0.001), located in the South (54.7% vs. 39.5%, p<0.001), and had Medicare coverage (32.8% vs. 15.0%, p<0.001)
 - RCI treated patients had less severe disease based on Charlson Comorbidity Index (1.32 ± 1.59 vs. 2.31 ± 1.89, p<0.001), and lower proportion of patients with cardiovascular/circulatory (57.7% vs. 66.5%, p<0.001) and mental health (19.2% vs. 27.2%, p<0.001) related comorbidities
 - Quality of care metrics were significantly lower for proportion of patients with claims for blood test (48.8% vs. 77.3%, p<0.001), while chest x-rays (6.3% vs. 0.0%, p<0.001), lung function testing (37.1% vs. 30.7%, p=0.012), and use of oxygen (8.7% vs. 5.6%, p=0.027) were higher in RCI patients compared to fourth line, respectively
- RCI Above Average vs. Below Average Adherence:** Baseline characteristics were similar overall for the RCI Adherence cohorts. The above average cohort had fewer Hispanics (3.3% vs. 7.6%, p=0.009) and patients with lung function testing (32.8% vs. 43.0%, p=0.005), with more patients having Medicare insurance coverage (37.5% vs. 26.4%, p=0.002)

Table 2: Baseline treatments of interest

	RCI vs. Fourth Line		RCI Adherence Sample		P-value ⁴	
	All RCI	Fourth line ²	Above average ³	Below average ³		
	(N = 735)	(N = 626)	(N = 421)	(N = 314)		
Treatments						
Corticosteroids (CS)						
Patients with ≥ 1 GC prescription, N (%)	585 (79.6%)	350 (55.9%)	<0.001	334 (79.3%)	251 (79.9%)	0.841
Intermittent use (< 60 days)	138 (18.8%)	151 (24.1%)	0.016	82 (19.5%)	56 (17.8%)	0.573
Low dose (≤ 7.5 mg/day)	59 (8.0%)	88 (14.1%)	<0.001	32 (7.6%)	27 (8.6%)	0.622
Medium dose (>7.5 and <15 mg/day)	58 (7.9%)	56 (8.9%)	0.484	42 (10.0%)	16 (5.1%)	0.015
High dose (>15 mg/day)	73 (9.9%)	65 (10.4%)	0.783	36 (8.6%)	37 (11.8%)	0.147
Number of CS prescriptions, Mean ± SD	0.37 ± 0.92	0.51 ± 1.13	0.252	0.38 ± 0.91	0.35 ± 0.93	0.806
Maximum CS dose (mg), Mean ± SD	2.84 ± 7.18	4.23 ± 10.75	0.202	2.83 ± 7.32	2.85 ± 7.00	0.987
Average daily dose (mg), Mean ± SD	2.36 ± 5.78	3.38 ± 8.74	0.248	2.35 ± 5.82	2.38 ± 5.75	0.976
Extended use (≥ 60 days)	447 (60.8%)	199 (31.8%)	<0.001	252 (59.9%)	195 (62.1%)	0.538
Low dose (≤ 7.5 mg/day)	253 (34.4%)	157 (25.1%)	<0.001	142 (33.7%)	111 (35.4%)	0.647
Medium dose (>7.5 and <15 mg/day)	305 (41.5%)	108 (17.3%)	<0.001	176 (41.8%)	129 (41.1%)	0.844
High dose (>15 mg/day)	231 (31.4%)	94 (15.0%)	<0.001	124 (29.5%)	107 (34.1%)	0.182
Number of CS prescriptions, Mean ± SD	3.92 ± 4.38	2.23 ± 3.98	<0.001	3.84 ± 4.36	4.03 ± 4.40	0.649
Maximum CS dose (mg), Mean ± SD	9.32 ± 10.01	4.97 ± 10.87	<0.001	9.07 ± 10.03	9.67 ± 9.99	0.530
Average daily dose (mg), Mean ± SD	6.72 ± 6.77	3.03 ± 5.66	<0.001	6.65 ± 6.93	6.80 ± 6.56	0.816
Patients with ≥ 1 other non-biologic DMARD prescription, N (%)	67 (9.1%)	97 (15.5%)	<0.001	34 (8.1%)	33 (10.5%)	0.257
Total filled per patient with ≥ 1 DMARD prescription	0.41 ± 1.72	0.74 ± 2.36	0.239	0.39 ± 1.75	0.44 ± 1.67	0.905
Concomitant therapies, N (%)						
Antihistamatics	444 (60.4%)	203 (32.4%)	<0.001	254 (60.3%)	190 (60.5%)	0.961
Antidepressants	284 (38.6%)	203 (32.4%)	0.017	173 (41.1%)	111 (35.4%)	0.114
Antineoplastic agents	165 (22.4%)	136 (21.7%)	0.749	91 (21.6%)	74 (23.6%)	0.531
Bisphosphonates	55 (7.5%)	31 (5.0%)	0.056	34 (8.1%)	21 (6.7%)	0.479
Corticosteroids	585 (79.6%)	350 (55.9%)	<0.001	334 (79.3%)	251 (79.9%)	0.841
Immunosuppressive agents	102 (13.9%)	64 (10.2%)	0.040	58 (13.8%)	44 (14.0%)	0.927
NSAIDs	246 (33.5%)	159 (25.4%)	0.001	132 (31.4%)	114 (36.3%)	0.159
Prescriptions, Mean ± SD						
Total prescriptions filled per patient	59.42 ± 46.90	46.22 ± 48.24	<0.001	60.57 ± 49.14	57.89 ± 43.74	0.444
Total number of unique drugs used	22.83 ± 14.74	17.89 ± 15.57	<0.001	22.70 ± 14.82	23.01 ± 14.67	0.778

Baseline treatments of interest

- RCI vs. Fourth Line:** The RCI cohort had a greater proportion of patients using CS overall (89.6% vs. 55.9%, p<0.001), driven by the high proportion of patients on extended use (≥60 days) CS therapy (60.8% vs. 31.8%, p<0.001) at all dose levels (p<0.001 for all) compared to the fourth line cohort.
 - The RCI cohort had fewer patients with intermittent CS use overall (18.8% vs. 24.1%, p=0.016) and the intermittent low dose group (8.0% vs. 14.1%, p<0.001)
 - The maximum CS dose and average daily dose (ADD) was significantly higher in the RCI cohort compared to fourth line cohort at baseline (9.32 ± 10.01mg vs. 4.97 ± 10.87mg, p<0.001) and (6.72 ± 6.77mg vs. 3.09 ± 5.66mg, p<0.001), respectively
 - RCI patients also had higher baseline use of other concomitant therapies like antihistamatics (60.4% vs. 32.4%, p<0.001), antidepressants (38.6% vs. 32.4%, p=0.017), immunosuppressive agents (13.9% vs. 10.2%, p=0.040), and NSAIDs (33.5% vs. 25.4%, p=0.001)
 - Medication use was higher overall at baseline for patients in the RCI cohort with higher mean total prescriptions filled (59.42 ± 46.90 vs. 46.22 ± 48.24, p<0.001) and total number of unique drugs tried (22.83 ± 14.74 vs. 17.89 ± 15.57, p<0.001)
- RCI Above Average vs. Below Average Adherence:** Baseline CS use, and other concomitant medication, were generally similar for the above average and below average adherence cohorts. The only significant difference at baseline was a higher proportion of patients in the intermittent medium dose CS use for above average cohort compared to below average (10.0% vs. 5.1%, p=0.015)

Change in corticosteroid use after treatment

Figure 1. Corticosteroid use, change from baseline: (A) RCI vs. fourth Line (B) RCI above average vs. below average adherence

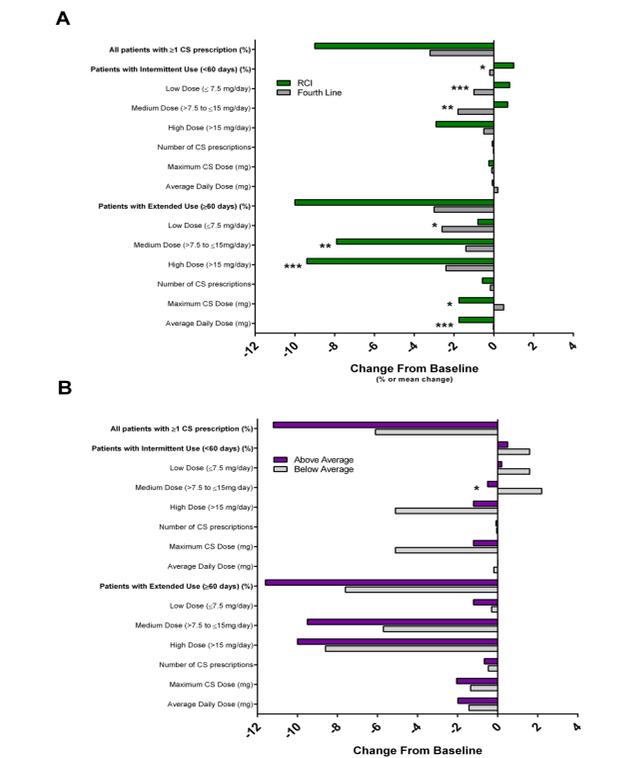
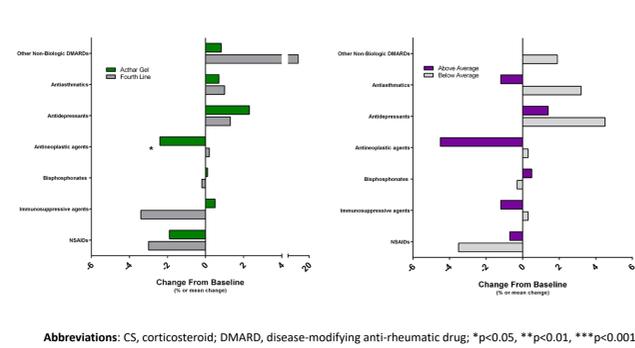


Figure 2. Use of other treatments of interest, change from baseline



Benefits of treatment and above average adherence

- RCI vs. Fourth Line:** The RCI cohort had a higher steroid burden at baseline and saw the greatest reduction in GC use, compared to the fourth line cohort.
 - After treatment, the RCI cohort had a larger proportion of patients that reduced CS use in the follow-up period (-9.0% vs. -3.2%)
 - The RCI cohort had an increase in intermittent use overall (1.0% vs. -0.2%, p=0.006), at the low (0.8% vs. -1.0%, p<0.001) and medium doses (0.7% vs. -1.8%, p=0.006), compared to fourth line
 - Extended CS use decreased by 10% after RCI treatment, compared to 3% in the fourth line cohort
 - RCI patients saw reductions at the extended CS medium (-7.9% vs. -1.4%, p<0.001) and high doses (-9.4% vs. -2.4%, p<0.001), with a significantly lower reduction at the low dose (-0.8% vs. -2.6%, p=0.011), compared to the fourth line cohort
 - The RCI treated cohort had a significant reduction in the maximum CS dose (-1.75mg vs. 0.50mg, p=0.017) and average daily dose (-1.75mg vs. -0.02mg, p<0.001) compared to fourth line

- RCI Above Average vs. Below Average Adherence:** Comparison between the RCI above average and below average cohorts demonstrates a clear trend of greater CS burden reduction with above average adherence
 - A greater proportion of patients in the above average cohort reduced CS use after treatment (-11.2% vs. -6.1%), with a significant difference at the intermittent medium dose (-0.5% vs. 2.2%, p=0.44)
 - Above average adherence resulted in greater reduction of extended CS use (-9.5% vs. -5.7%), and high dose compared to below average
 - The above average cohort had greater reduction in maximum CS dose (-2.05mg vs. -1.35mg) and average daily dose (-1.98mg vs. -1.43mg)

Discussion and conclusions

- This study indicates the benefits of RCI therapy on the reduction of CS burden in the treatment of symptomatic sarcoidosis for RCI patients overall, and with the greatest benefit observed for those with above average adherence. Reduction in overall steroid burden is associated with improved HRQoL measures for fatigue, daily activities, and general satisfaction
- RCI Overall:** Treatment with RCI demonstrated a steroid sparing effect, with greater reductions in proportion of patients using CS, those with extended CS use at all dose levels, the maximum CS dose, and mean ADD in the follow-up period, compared to similar treatments per ERS guidelines
- RCI Adherence:** Higher adherence to RCI resulted in greater reductions in CS use compared to those below the mean PDC of the full cohort

References

- Gerke, A. K., et al. (2017). "Disease Burden and Variability in Sarcoidosis." *Annals of the American Thoracic Society* 14(Supplement_6): S421-S428.
- Judson, M. A., et al. (2015). "The effect of corticosteroids on quality of life in a sarcoidosis clinic: The results of a propensity analysis." *Respiratory Medicine* 109(4): 526-531.
- Sharp, M., et al. (2020). "Association of Medication Adherence and Clinical Outcomes in Sarcoidosis." *Chest* 158(1):226-233.
- Acthar® Gel. Package Insert. Mallinckrodt ARD LLC; 2021
- Baughman, R. P., et al. (2021). "ERS clinical practice guidelines on treatment of sarcoidosis." *European Respiratory Journal* 58(6): 2004079.
- Rahaghi, F. F., et al. (2020). "Delphi consensus recommendations for a treatment algorithm in pulmonary sarcoidosis." *European Respiratory Review* 29(155): 190146.