H.P. Acthar® Gel Overview

Mallinckrodt Pharmaceuticals

- Current U.S. Indications

  H.P. Acthar Gel (repository corticotropin injection)

  - **Infantile spasms:** As monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.
  - **Multiple Sclerosis**: As treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown H.P. Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease.
  - **Rheumatic Disorders:** As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis; Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), Ankylosing spondylitis.
  - **Collagen Diseases:** During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).
  - **Dermatologic Diseases:** Severe erythema multiforme, Stevens-Johnson syndrome.
  - **Allergic States:** Serum sickness.
  - **Ophthalmic Diseases:** 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; anterior segment inflammation.
  - **Respiratory Diseases:** Symptomatic sarcoidosis.
  - **Edematous State:** To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

H.P. Acthar® Gel Overview

Mallinckrodt Pharmaceuticals

▶ Target Audiences, Market Size, Current Market Penetration

Diagnosis	Target Audience	Fiscal 2016 Acthar Addressable Patients	Fiscal 2016* Treated Patients	Acthar Penetration Rate
Multiple Sclerosis Relapse	Neurologists	26,456	4,829	18%
Infantile Spasms	Child Neurologists	1,500	797	53%
Proteinuria Remission in Idiopathic Nephrotic Syndrome	Nephrologists	12,156	1,494	12%
Rheumatoid Arthritis (adjuvant therapy)	Rheumatologists	84,332	1,492	2%
SLE (Lupus)	Rheumatologists	76,170	1,043	1%
Dermatomyositis (Polymyositis)	Rheumatologists (Dermatologists, Neurologists)	20,000	849	4%
Psoriatic Arthritis	Rheumatologists	27,000	174	1%
Symptomatic Sarcoidosis	Pulmonologists	22,000	506	2.3%
Ankylosing Spondylitis	Rheumatologists	49,080	43	0.1%

***Estimated**

▶ Current Sponsored Clinical Trials Listed on ClinicalTrials.gov

NCT	Title	Phase	# Subjects
NCT01601236	Acthar for Treatment of Proteinuria in Diabetic Nephropathy Patients	2	34
NCT01906658	Study to Explore Safety and Tolerability of Acthar in Patients With Amyotrophic Lateral Sclerosis	2A	43
NCT01753401	Acthar for the Treatment of Systemic Lupus Erythematosus in Patients With a History of Persistently Active Disease	4	38
NCT01386554	Acthar for Treatment of Proteinuria in Membranous Nephropathy Patients (CHART)	4	60

H.P. Acthar® Gel Company-Sponsored Data Generation Pipeline

Mallinckrodt Pharmaceuticals

Neurology

	MOA	Clinical	HEOR
MS Relapse	√	√	√
Infantile Spasms			√
ALS		√	

Rheumatology

	MOA	Clinical	HEOR
SLE (Lupus)	√	√	√
Rheumatoid Arthritis	√		√
PM/DM			√

Remission of Proteinuria

	MOA	Clinical	HEOR
iMN	√	√	√
FSGS	√	√	√
Diabetic Nephropathy		√	

Respiratory

	MOA	Clinical	HEOR
Symptomatic Sarcoidosis			√

Ophthalmology

	MOA	Clinical	HEOR
Ocular Inflammation	√		√

ALS: Amyotrophic Lateral Sclerosis, FSGS: Focal Segmental Glomerulosclerosis, HEOR: Health Economic Outcomes Research; iMN: idiopathic Membranous Nephropathy, MOA: Mechanism of Action, MS: Multiple Sclerosis , PM/DM: Polymyositis/Dermatomyositis, SLE: Systemic Lupus Erythematosus

Repository Corticotropin Injection (H.P. Acthar® Gel) Attenuates Disease Activity in Patients with Persistently Active Systemic Lupus Erythematosus (SLE) Requiring Corticosteroids

Richard A. Furie[1], Enxu Zhao[2], Maya Das[2], Daner Li[2], Shanique Smythe[2], Ericka Mathura[2] and Patrice M. Becker[2]

[1]Hofstra North Shore LIJ School of Medicine, North Shore LIJ Health System, Great Neck, NY 11030; [2]Mallinckrodt Pharmaceuticals, Inc; Ellicott City, MD 21043

ABSTRACT

Background/Rationale: Melanocortins such as corticotropin and alpha-MSH may modulate steroid-independent immune responses relevant to SLE pathophysiology. We previously reported that repository corticotropin injection (RCI), an FDA approved melanocortin therapeutic, attenuated B cell development, circulating autoantibody titers, and disease activity in a murine SLE model, supporting the efficacy of RCI as a treatment alternative for patients with SLE.

Methods: This 8 wk double-blind randomized placebo-controlled study assessed clinical efficacy of RCI in patients with persistently active SLE despite moderate dose corticosteroids. The primary objective was to explore the effects of RCI on the Hybrid SLE Disease Activity Index (hSLEDAI), with key secondary objectives to evaluate effects on British Isles Lupus Assessment Group-2004 (BILAG), Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), and 28-joint count score. Patients were eligible if they had persistently active SLE (hSLEDAI >2) with arthritis and/or skin involvement and BILAG A or B in mucocutaneous and/ or musculoskeletal systems despite 7.5-30 mg prednisone daily for ≥ 4 wk prior to screening. 38 subjects were randomized to receive SC RCI 80 U every other day (RCI80; n=13) or 40 U daily (RCI40; n=13), or SC Placebo gel (n=12). Study medication was maintained at the assigned regimen for 4 wk, then tapered over 4 wk to 2x/wk administration of the assigned dose. Clinical response was assessed by change from baseline for hSLEDAI (wk 2, 4, 6 & 8), BILAG, CLASI, and Tender & Swollen Joint Count (wk 4 & 8).

Results: Mean hSLEDAI scores at baseline were 9.8±2.1, 8.7±2.9, 11.3±3.3, and 10.0±3.3 in the Placebo, RCI40, RCI80, and combined RCI groups, respectively (mean ±SD). Baseline BILAG and CLASI scores were similar between groups, though tender swollen joint count was higher in subjects randomized to RCI80 vs RCI40 or Placebo (p≤ 0.05). RCI led to significant improvement in key efficacy endpoints compared with Placebo, including total hSLEDAI and BILAG scores, CLASI Activity, and Tender & Swollen Joint Count. There were no significant differences in the incidence of treatment-emergent adverse events between groups.

Activity index change from baseline	Time	Placebo LS mean (SE)	RCI 40U QD LS mean (SE)	RCI 80U QOD LS mean (SE)	RCI (combined) LS mean (SE)
hSLEDAI	4 wk	-1.2 (0.6)	-1.2 (0.6)	-2.1 (0.6)	-1.6 (0.4)
	6 wk	-1.4 (0.7)	-2.9 (0.7) *p=0.045	-3.5 (0.7)* *p=0.045	-3.2 (0.5)* *p=0.040
	8 wk	-0.8 (0.9)	-3.7 (0.9)* *p=0.026	-3.9 (0.9)* *p=0.020	-3.8 (0.6)* *p= 0.008
BILAG	4 wk	-4.7 (1.6)	-5.2 (1.5)	-7.2 (1.6)	-6.1 (1.1)
	8 wk	-1.8 (1.5)	-8.1 (1.4)* *p=0.005	-9.3 (1.4)* *p=0.002	-8.6 (1.0)* *p=0.001
CLASI Activity	4 wk	-0.2 (0.7)	-2.2 (0.7)* *p=0.051	-1.7 (0.7)	-2.0 (0.5)* *p=0.050
	8 wk	-0.6 (1.0)	-3.7 (1.0)* *p=0.030	-2.3 (1.1)	-3.1 (0.7)* *p=0.047
Tender & Swollen Joint Ct	4 wk	-2.5 (0.8)	-2.3 (0.7)	-3.5 (0.8)	-2.8 (0.5)
	8 wk	-2.5 (0.5)	-2.8 (0.5)	-4.4 (0.6)* *p=0.019	-3.5 (0.4)

Conclusions: These data demonstrate that RCI reduces disease activity in patients requiring corticosteroids for persistently active SLE, and that improvements occur within 8 wk of treatment initiation. The tolerability, steroid-sparing effects, and impact of RCI on long-term disease control are being further evaluated in an ongoing open-label extension of this study.

INTRODUCTION

- Unmet medical need remains for therapies to safely reduce disease activity in SLE patients, particularly those who are intolerant of or unresponsive to standard medications
- Repository corticotropin injection (RCI) is approved by the FDA for use during an exacerbation or as maintenance therapy in selected cases of SLE [1]
- The primary active ingredient in RCI is a porcine adrenocorticotropic hormone (ACTH) analogue. ACTH binds all five known melanocortin receptors (MC1-5R) [2] and thus may have biologic activity beyond stimulation of adrenal corticosteroid production. MC1, 3, 4 and 5R are expressed on multiple leukocytes subpopulations (e.g. T & B cells, macrophages), as well as within target organs (e.g. skin, kidney, CNS) relevant to SLE [3]
- Experimental evidence suggests that MCR ligands such as ACTH and **α**-MSH may possess steroid-independent anti-inflammatory and immune modulatory activity relevant to SLE pathophysiology [4,5]. We previously demonstrated that RCI attenuated B cell development, circulating autoantibody titers, and disease activity in a murine SLE model (the F1 hybrid of the New Zealand Black and New Zealand White strains; NZB/W F1) [5]. Additional data suggests that RCI, but not Placebo, attenuated IL4/CD40L-induced proliferation and immunoglobulin production in B lymphocytes isolated from healthy human volunteers [6]

References

1. H.P. Acthar® Gel Prescribing Information.
2. Mucenieice R, Larsson M, Wikberg JES. The melanocortin 1, 3, 4, or 5 receptors do not have a binding epitope for ACTH beyond the sequence of α-MSH. Journal of Endocrinology 1997; 155:73-78.
3. Catania A, Gatti S, Colombo G, Lipton JM. Targeting melanocortin receptors as a novel strategy to control inflammation. Pharmacol Rev 2004; 56:1-29.
4. Botte DA,, Noronha IL, Malheiros DMAC, Peixoto TV, SBV de Mello. Alpha-melanocyte stimulating hormone ameliorates disease activity in an induced murine lupus-like model. Clin Exp Immunol 2014; 177:381-390.
5. Decker D, Grant C, Oh L, Becker P, Young D, Jordan S. Immunomodulatory effects of H. P. Acthar Gel on B cell development in the NZB/W F1 mouse model of systemic lupus erythematosus. Lupus 2014; 23:802-12
6. Olsen NJ, Decker D, Higgins P, Becker PM, McAloose CA, Benko AL, Kovacs WJ. Direct effects of HP Acthar gel on human B lymphocyte activation in vitro. Arthritis Research & Therapy 2015; 17:300.

OBJECTIVE

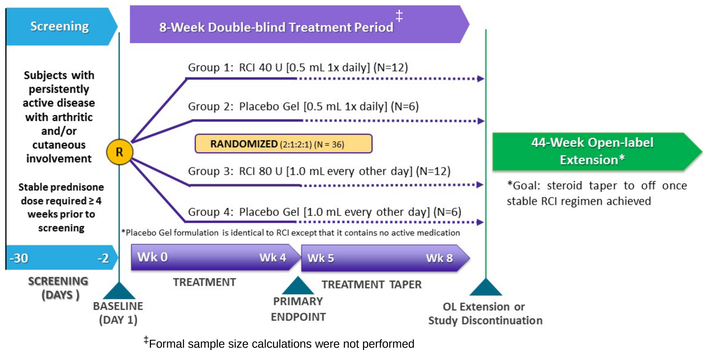
This pilot study (NCT01753401) was designed to confirm the hypothesis that RCI added to standard of care would improve measures of disease activity in SLE patients requiring moderate dose corticosteroids for persistently active disease involving skin and/or joints

STUDY POPULATION

Key eligibility criteria:

- Adults with persistently active SLE with arthritic and/or cutaneous involvement as demonstrated by Hybrid SLEDAI (hSLEDAI) score ≥ 2 **and** moderate to severe rash and/or arthritis as demonstrated by BILAG 2004 score A or B in the mucocutaneous and/or musculoskeletal systems
- Persistent disease activity despite a stable dose of prednisone (7.5 to 30 mg/day of prednisone or equivalent within the 4 wk prior to screening)
- Documented history of positive antinuclear antibody (ANA) and of autoantibodies to at least one of the following: anti-dsDNA, anti-Smith, or anti-cardiolipin
- Use of antimalarials, NSAIDs (stable regimen within the 4 weeks prior to screening), as well as methotrexate, azathioprine, and mycophenolate mofetil (stable regimen within the two months prior to screening) was allowed

STUDY DESIGN



‡Formal sample size calculations were not performed

OUTCOME MEASURES*

Primary endpoint*:

• Proportion of patients meeting responder definition at Week 4, defined as decrease in hSLEDAI score from 4 to 0 for arthritis and no BILAG worsening in other organ systems, **OR** a decrease in hSLEDAI score from 2 to 0 for rash and no BILAG worsening in other organ systems

Key secondary endpoints*:

• Proportion of patients meeting responder definition at Week 8
• Change from baseline in hSLEDAI at Weeks 2, 4, 6, and 8
• Change from baseline in total BILAG score at Weeks 4 and 8
• Proportion of patients achieving BILAG improvement (A at baseline to B/C/D at Weeks 4 and 8, or B at baseline to C/D at Weeks 4 and 8) in mucocutaneous or musculoskeletal body systems
• Change from baseline in tender and swollen joint counts at Weeks 4 and 8
• Change from baseline in cutaneous lupus activity as measured by the CLASI at Weeks 4 and 8

Key Exploratory endpoint:

• Proportion of patients that met the definition of SLE Responder Index (SRI) at Weeks 4 and 8

Safety endpoints:

• AEs and SAEs, abnormal clinical laboratory tests, physical examinations and ECGs

Statistical analyses:

• mITT (modified intent to treat) population (defined as all randomized patients who received at least one dose of study medication and contributed any post-baseline efficacy or safety data) was the primary population for efficacy and safety analyses
• Analysis of primary endpoint was performed using an exact logistic regression model with treatment group (3 levels: RCI 40 U QD, RCI 80 U QOD, and combined placebo) as a factor. Comparisons were made between each RCI group and combined Placebo, and between the combined RCI groups and combined Placebo
• All quantitative secondary endpoints were analyzed using ANCOVA models with treatment group (3 levels: RCI 40 U QD, RCI 80 U QOD, combined placebo) as a factor and the baseline value of the corresponding endpoint as a covariate; data are reported as least square (LS) means and LS mean differences between groups
• Secondary endpoints that are proportions were analyzed using Fisher's exact tests
• Exploratory analyses were conducted using an exact logistic regression model with treatment group as a factor

*All investigators were required to complete training for outcome assessment measures prior to study start

RESULTS

Table 1. Baseline demographics and disease characteristics mITT population

Parameter		Combined Placebo (n=11)	RCI 40U QD (n=13)	RCI 80 U QOD (n=12)	Combined RCI (n=25)
Age (yr)	Mean (SD)	39.1 (9.1)	42.6 (12.7)	43.2 (7.2)	42.9 (10.2)
Female	n (%)	10 (90.9)	12 (92.3)	12 (100)	24 (92.3)
Caucasian/African American	n (%)	5 (45.5)/6 (54.5)	9 (69.2)/3 (23.1)	9 (75.0)/ 3 (25.0)	18 (72.0)/6 (24.0)
Hybrid SLEDAI*	Mean (SD)	9.8 (2.1)	8.7 (2.9)	11.3 (3.3)	10.0 (3.3)
BILAG (global score)	Mean (SD)	15.4 (9.6)	13.1 (6.6)	18.6 (3.4)	15.7 (5.9)
CLASI (total activity)	Mean (SD)	6.1 (6.6)	5.9 (7.0)	7.0 (5.8)	6.4 (6.3)
Tender & Swollen Joint Count	Mean (SD)	4.2 (4.8)	2.9 (3.4)	8.6 (6.8)	5.6 (6.0)
Physician Global Assessment (PGA) (mm)	Mean (SD)	52.6 (12.5)	52.9 (14.3)	55.9 (11.9)	54.4 (13.0)
Anti-ds DNA > 5 IU/mL	n (%)	6 (54.5)	9 (69.2)	6 (50.0)	15 (57.7)
C3 < 0.87 g/L	n (%)	3 (27.3)	3 (23.1)	4 (33.3)	7 (26.9)
C4 < 0.19 g/L	n (%)	6 (54.5)	6 (46.2)	2 (16.7)	8 (32.0)
Prednisone (mg/day)	Mean (SD)	16.4 (8.09)	10.8 (2.58)	9.2 (1.23)	10.0 (2.17)
Antimalarials	n (%)	8 (72.7)	11 (84.6)	7 (58.3)	18 (72.0)
Immunosuppressants	n (%)	6 (54.5)	4 (30.8)	2 (16.7)	6 (23.1)

*The most common hSLEDAI descriptors in the overall population at baseline were arthritis (83.3%), alopecia (80.6%), and rash (75.0%)

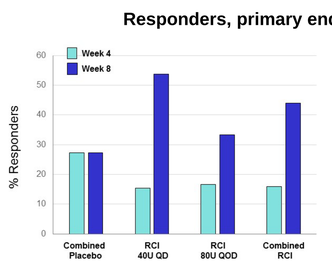


Figure 1. Percent responders, as defined for primary endpoint, at Weeks 4 & 8. No significant differences were seen in the proportion of responders at Week 4 for RCI (40U QD, n=13; 80U QOD, n=12; or combined RCI, n=25) as compared with combined Placebo (n=11). The proportion of responders in RCI treated groups increased at Week 8 (RCI 40U QD, n=12; RCI 80U QOD, n=10; combined RCI, n=22; combined Placebo, n=11) although this increase did not achieve statistical significance. Responders were defined by decrease in hSLEDAI score from 4 to 0 for arthritis or a decrease in hSLEDAI score from 2 to 0 for rash and no BILAG worsening in other organ systems.

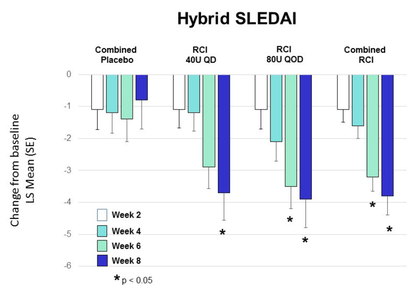


Figure 2. hSLEDAI change from baseline at Weeks 2, 4, 6 and 8. No statistically significant changes from baseline were seen in hSLEDAI at Weeks 2 or 4, but by Week 6, hSLEDAI decreased significantly from baseline in the RCI 80U QOD and combined RCI groups as compared to the combined Placebo group. By Week 8, a statistically significant improvement in hSLEDAI was seen with both RCI doses and the combined RCI group as compared with combined Placebo. Data shown represent LS Mean ± SE.

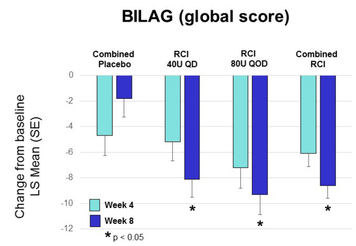


Figure 3. BILAG 2004 (global score) change from baseline at Weeks 4 and 8. No statistically significant differences between treatment groups were seen in change from baseline of global BILAG score at Week 4. By Week 8 BILAG scores were significantly improved from baseline in both RCI dose groups and the combined RCI group as compared with the combined Placebo group. The proportion of patients achieving BILAG improvement in mucocutaneous or musculoskeletal body systems at Weeks 4 and 8 was numerically higher in the RCI groups as compared to the combined Placebo group, and a statistically significant difference was achieved for the RCI 80 U QOD group compared to combined Placebo cohort at Week 8 (data not shown). Data shown represent LS Mean ± SE.

Table 2. Proportion of Patients Achieving Improvement in BILAG Category for Mucocutaneous or Musculoskeletal Domains at Weeks 4 and 8

Time point	Statistics	Combined Placebo N=11	RCI 40U QD N=13	RCI 80U QOD N=12	Combined RCI N=25
Week 4	Improvement* n(%) No Improvement n(%) *P* value	3 (27.3) 8 (72.7)	5 (38.5) 8 (61.5) 0.679	8 (66.7) 4 (33.3) 0.100	13 (52.0) 12 (48.0) 0.277
Week 8	Improvement* n(%) No Improvement n(%) *P* value	4 (36.4) 7 (63.6)	7 (53.8) 6 (46.2) 0.444	10 (83.3) 2 (16.7) 0.036	17 (68.0) 8 (32.0) 0.141

* Improvement defined as category A at baseline to B/C/D or B at baseline to C/D at Week 4 or 8
Missing data classified as "No improvement"

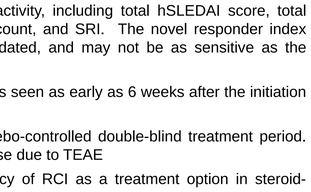


Figure 4. CLASI Activity score change from baseline at Weeks 4 and 8. Significant improvement was noted in CLASI Activity scores, assessed as change from baseline, when comparing RCI 40 U QD and the combined RCI group with the combined Placebo group. No statistically significant changes were noted when comparing RCI 80 U QOD to combined Placebo, though the data trend was similar. Data shown represent LS Mean ± SE.

Figure 5. Tender & Swollen Joint count change from baseline at Weeks 4 and 8. Significant improvement was noted in Tender & Swollen Joint count, assessed as change from baseline, when comparing RCI 80 U QOD with the combined Placebo group at Week 8. Data shown represent LS Mean ± SE.

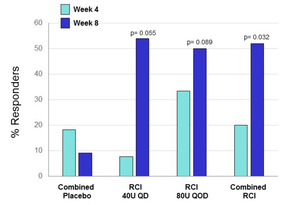


Figure 6. SRI: Responder rate defined by SRI at Weeks 4 & 8. No statistically significant differences were seen in the SRI at Week 4 for RCI vs combined Placebo (n=10). However, there was a notable trend for increased number of subjects meeting the definition of response by SRI in both RCI dose groups as compared with combined Placebo at Week 8. At week 8, the number of subjects achieving response based on SRI was significantly greater in the combined RCI vs combined Placebo groups. Number of subjects/group with baseline hSLEDAI ≥ 4 and data to calculate SRI at Week 8: RCI 40U QD, n=12; RCI 80U QOD, n=10; combined RCI, n=22; combined Placebo, n=11

Table 3. Overall Summary of Treatment-Emergent Adverse Events

	Combined Placebo N=11	RCI 40U QD N=13	RCI 80U QOD N=12	Combined RCI N=25
Category	**Patients N (%)**	**Patients N (%)**	**Patients N (%)**	**Patients N (%)**
Any TEAE	9 (81.8)	12 (92.3)	7 (58.3)	19 (76.0)
Any severe TEAE*	1 (9.1)	0	1 (8.3)	1 (4.0)
Any treatment-related AE	4 (36.4)	7 (53.8)	4 (33.3)	11 (44.0)
Any TEAE leading to study discontinuation	0	3 (23.1)	1 (8.3)	4 (16.0)
Any serious TEAE	0	2 (15.4)	1 (8.3)	3 (12.0)
Any TEAE resulting in death	0	0	1 (8.3)	1 (4.0)

AE = adverse event; AEs classified into system organ class and preferred terms using MEDRA v 15.1
*AEs were considered severe if the severity of an event was missing

No new safety signals were reported.

• There was one death on study in a patient in the RCI 80 U QOD group attributed to severe Klebsiella sepsis with multi-organ failure. All of the TEAEs leading to this death were considered by the Investigator to be unlikely related to the study medication
• 2 additional patients receiving RCI 40U QD experienced serious TEAEs, including moderate gastroesophageal reflux disease & moderate chest discomfort (reported as related to study medication), and moderate hemorrhagic ovarian cyst & moderate viral infection (reported as unrelated to study medication)

SUMMARY & CONCLUSIONS

- Although the primary endpoint of response (defined by complete resolution of skin or joint activity by hSLEDAI with no new organ system disease by BILAG) was not met, the addition of RCI to standard of care led to significant improvement in key measures of disease activity, including total hSLEDAI score, total BILAG score, CLASI activity score, tender and swollen joint count, and SRI. The novel responder index used as a primary endpoint for this study has not been validated, and may not be as sensitive as the established disease activity scales
- Significant improvement in key measures of disease activity was seen as early as 6 weeks after the initiation of RCI therapy
- 5/38 subjects did not complete the 8 week randomized, placebo-controlled double-blind treatment period. Two of these subjects discontinued during the double-blind phase due to TEAE
- Despite the small sample size, these data support the efficacy of RCI as a treatment option in steroid-dependent patients with persistently active SLE
- Preliminary assessment of the impact of RCI maintenance therapy on long-term disease control and the need for ongoing glucocorticoid therapy are being evaluated in an ongoing open-label extension of this signal study
- Data from this study will inform future clinical investigations of RCI in SLE

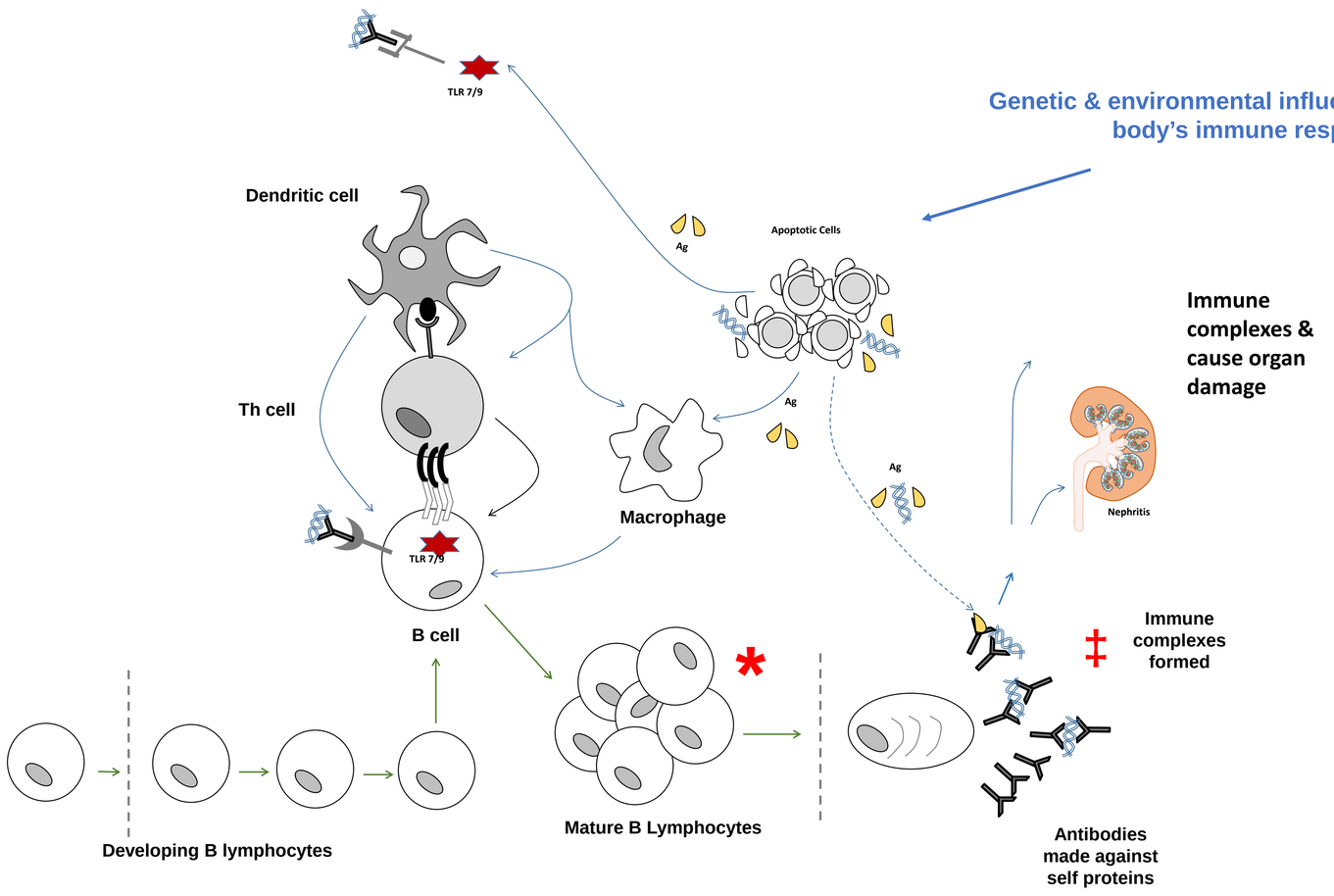
Author Disclosure Information: R. Furie is an Investigator and consultant for Mallinckrodt Pharmaceuticals, Inc, E. Zhao is a full time employee of Mallinckrodt Pharmaceuticals, M. Das, D. Li, S. Smythe, and E. Mathura are former employees of Mallinckrodt and own stock or stock options in Mallinckrodt Pharmaceuticals, and P.M. Becker is a full time employees and owns stock or stock options in Mallinckrodt Pharmaceuticals.

This study was sponsored by Mallinckrodt Pharmaceuticals and conducted by Mallinckrodt Pharmaceuticals and INC Research in compliance with accepted standards of Good Clinical Practice

Poster reprinted from the ACR/ARHP Annual Meeting held November 6-11, 2015. The American College of Rheumatology does not guarantee, warrant, or endorse any commercial products or services. Reprinted by Mallinckrodt Pharmaceuticals.

Nonclinical Support for H.P. Acthar® Gel as a Therapy for Systemic Lupus Erythematosus (SLE)

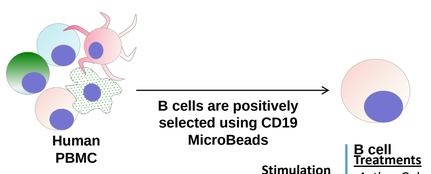
Key pathways implicated in the pathophysiology of SLE



- In SLE, the immune system recognizes self proteins as foreign, and responds to try to eliminate the foreign protein
- Many different immune cell types have been implicated in the immunopathogenesis of SLE, including B and T lymphocytes & antigen presenting cells (dendritic cells & macrophages)
- Nonclinical studies suggest melanocortin peptides and/or Acthar may attenuate multiple aspects of the immune response contributing to SLE pathophysiology

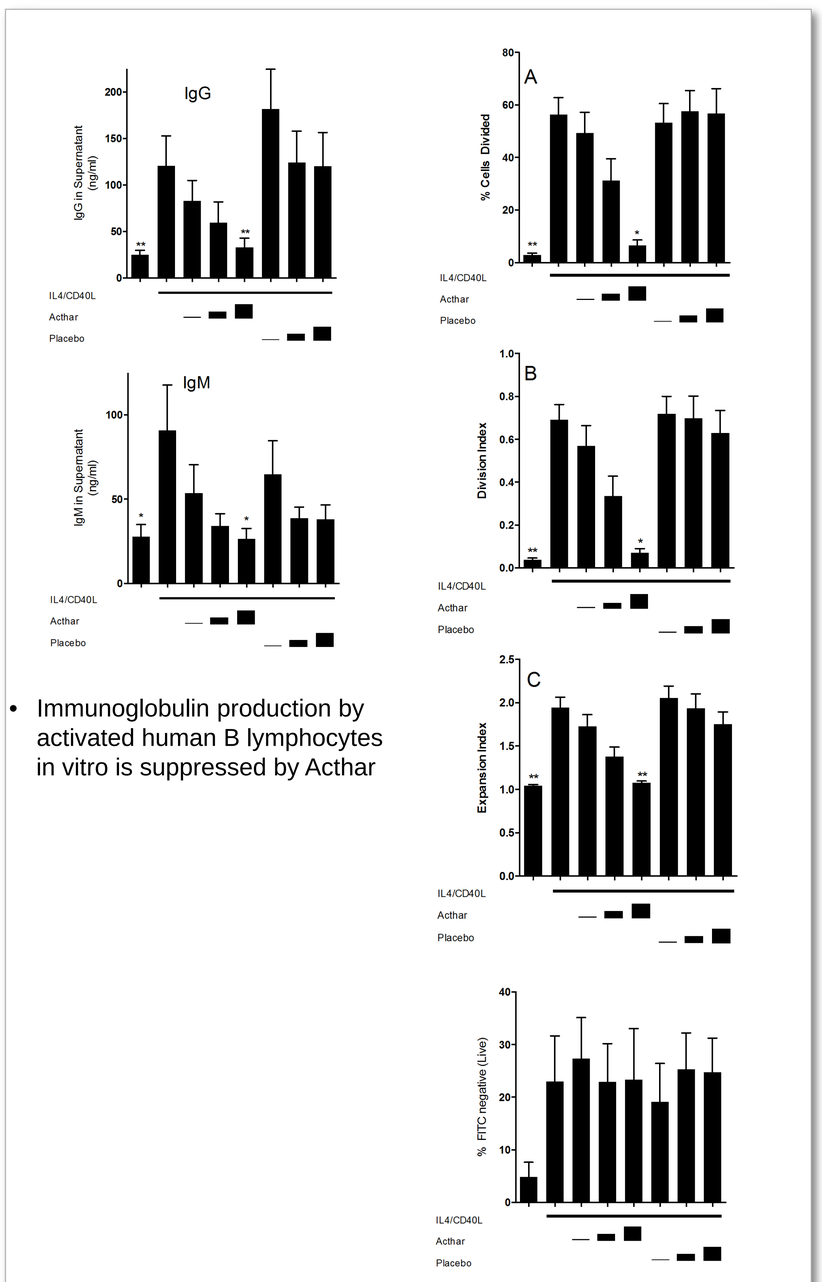
*Acthar directly attenuates activation and immunoglobulin production in B lymphocytes isolated from healthy human subjects

Methods



Culture B cells for 7 Days and measure:

- Cell proliferation (CSFE) and viability (trypan blue).
- Supernatant IgG and IgM antibody levels.



- Immunoglobulin production by activated human B lymphocytes in vitro is suppressed by Acthar
- Proliferation of activated human B lymphocytes *in vitro* is suppressed by Acthar, while B cell viability is unaffected

NJ Olsen, DA Decker, P Higgins, PM Becker, CA McAloose, AL Benko, WJ Kovacs. Direct effects of HP Acthar® Gel on human B lymphocyte activation in vitro. Arthritis Research & Therapy (2015) 17:300.

‡ Acthar was shown to attenuate auto-antibody production and end-organ damage in a mouse model of SLE

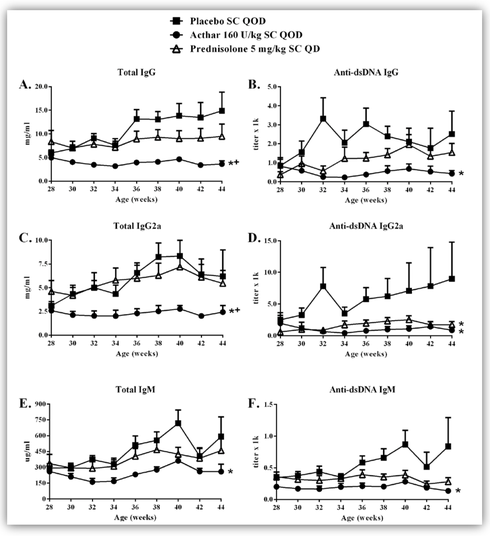
Methods

In Vivo and Terminal Readouts Collected During 28 to 46 weeks of age

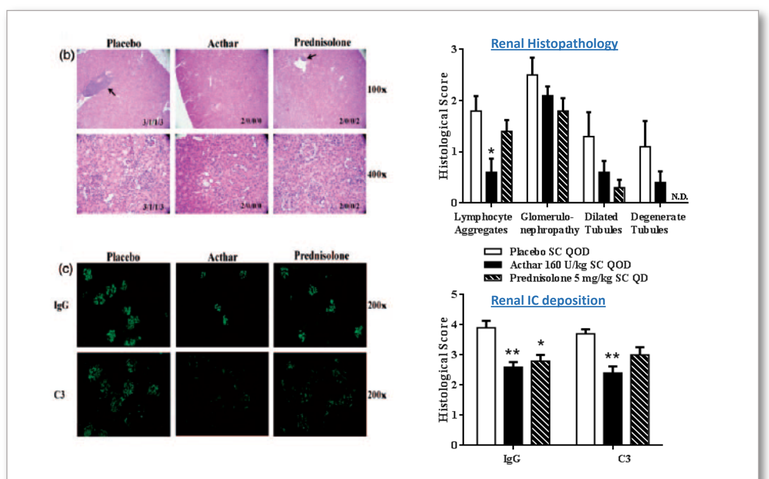
In-life Data:
- Proteinuria every two weeks
- Weekly body weight measurement
- Serum collection every two weeks and terminal bleed
  - Measure total antibodies (IgG, IgG2a, and IgM) and anti-dsDNA autoantibodies (IgG, IgG2a, and IgM)

Terminal Data:
- Gross necropsy
- Immunophenotyping of spleen cells via flow cytometry
- Renal Histopathology:
  - H & E: Blinded scoring of glomerulonephropathy, tubule dilation, tubule degeneration, and lymphocyte infiltration
  - Immune complex (IgG and C3) deposition

Euthanasia Criteria: ≥ 3+ proteinuria on two consecutive measurements, ≥ 20% body weight loss, or prostration



- Acthar treatment inhibited the increase in circulating immunoglobulins and anti-dsDNA antibodies seen in NZB/W F1 mice with established signs of autoimmune disease



- Acthar treated NZB/W F1 mice developed less severe proteinuria, and had less renal lymphocyte infiltration. In addition, Acthar treatment led to attenuation of immune complex deposition in the kidney

DA Decker, C Grant, L Oh, PM Becker, D Young, S Jordan. Immunomodulatory effects of H.P. Acthar® Gel on B cell development in the NZB/W F1 mouse model of systemic lupus erythematosus. Lupus (2014) 23: 802-812.

***The exact mechanism of action of Acthar is unknown, and further investigation is being conducted. This information is based on nonclinical data and the relationship to clinical benefit is unknown.**

Mallinckrodt Pharmaceuticals

Treatment of Proteinuria Due to Treatment Resistant or Treatment Intolerant Idiopathic Focal Segmental Glomerulosclerosis: A 2 Part Prospective Study of H.P. Acthar® Gel (The PODOCYTE Study)

Mallinckrodt Pharmaceuticals

Background

- Primary focal segmental glomerulosclerosis (FSGS) is a major cause of idiopathic nephrotic syndrome in adults and adolescents, and the most common primary glomerular disorder causing end-stage renal disease in the United States
- Primary FSGS is a progressive disorder; ~ 50% of affected patients develop end-stage renal disease over a period of 5-8 years
- Current treatments for primary FSGS are effective in < 50% patients and are associated with significant side effects
- Acthar is approved to induce a diuresis or a remission of proteinuria in idiopathic nephrotic syndrome
- Remission of proteinuria (complete or partial) in FSGS is associated with improved renal survival rate
- Data from a recently published case series suggest that 29% of subjects with steroid-resistant or steroid-dependent primary FSGS achieved complete or partial remission of proteinuria following treatment with Acthar

Purpose

- The purpose of this study is to provide nephrologists with additional clinical evidence regarding the efficacy and safety of Acthar in subjects with treatment-resistant or treatment-intolerant FSGS.

Objective

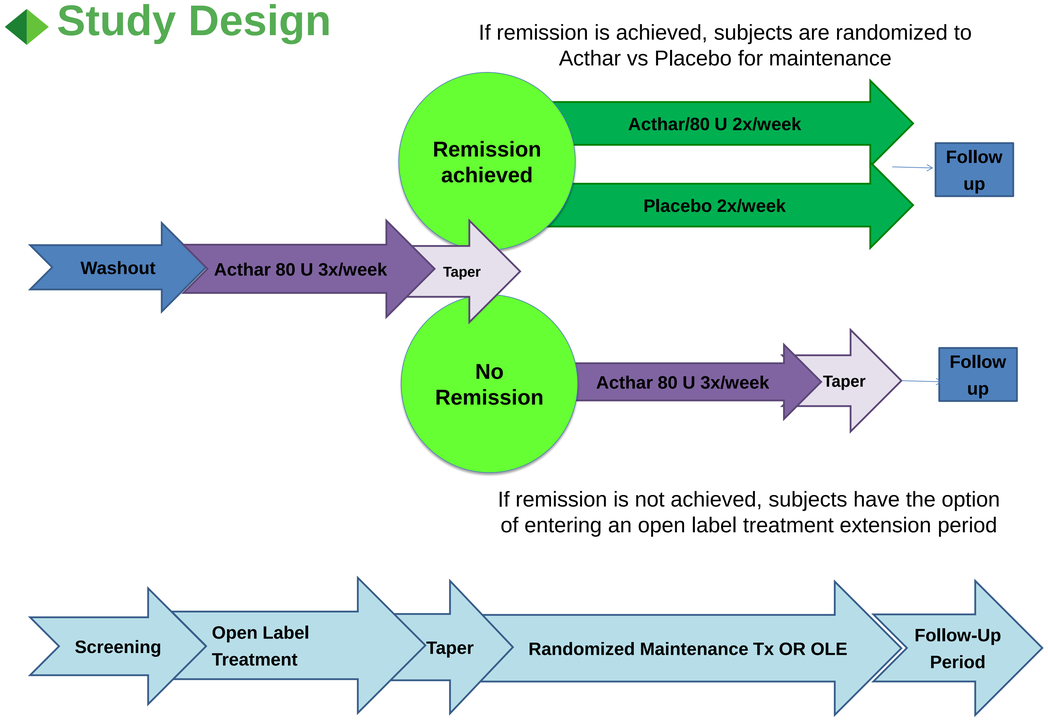
- The primary objective of this study is to confirm the efficacy of Acthar for the induction of remission of proteinuria in subjects with primary FSGS who are resistant to or intolerant of immunosuppressive therapies including, but not limited to, corticosteroids or CNIs.

.

Study Population

- Adult subjects with primary FSGS with nephrotic range proteinuria (uPCR > 3500 mg/g and eGFR > 30 mL/min/1.73m^2) who have failed to achieve complete or partial remission with or who are intolerant to ≥ 1 immunosuppressant
- Treatment with ACEi/ARB/DRI ≥ 4 weeks prior to Screening
- SPB ≤ 150 mmHg, DBP ≤ 90 mmHg

Study Design



Study Endpoints

Primary Endpoint

- Proportion of subjects that achieve remission of proteinuria at Week 24

Key Secondary Endpoints

- Time to first remission
- Proportion of subjects that maintain remission of proteinuria at Week 50 in Acthar-treated group vs. Placebo
- Proportion of subjects with remission of proteinuria at Week 24 who experience relapse during Randomized Maintenance Period in Acthar-treated group vs. Placebo
- Proportion of subjects with ≥ 50% reduction of proteinuria at Week 50 in Acthar-treated group vs. Placebo

Health Care Resource Use and Costs of Adrenocorticotropic Hormone in Relapses of Multiple Sclerosis

Ryan N. Hansen, PharmD, PhD[1]; Laura S. Gold, PhD[1]; Patricia Schepman, PharmD, PhD[3]; John Niewoehner, PharmD[2]; Michael Philbin, PharmD; MBA[2]; Kavitha Damal, PhD[2].
[1]*Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy, University of Washington, Seattle, WA;* [2]*Mallinckrodt Pharmaceuticals, St. Louis, MO;* [3]*Formerly at Mallinckrodt Pharmaceuticals, St. Louis, MO*

Abstract

Background

Multiple Sclerosis (MS) is an autoimmune, neuro-inflammatory disorder characterized by acute exacerbations ('relapses'), interspersed between remissions.[1] MS relapses impose a heavy economic burden on society and are commonly treated with intravenous methylprednisolone (IVMP). For patients who remain symptomatic despite first-line treatment and require an alternate treatment option, current therapeutic options include other hormonal therapies such as adrenocorticotropin hormone analogue (Acthar, H.P. Acthar® Gel), intravenous immunoglobulin (IVIG) and plasmapheresis (PMP).[2-8]

Objective

We explored the economic burden accrued among patients who remain symptomatic despite first-line treatment, comparing Acthar versus IVIG or PMP in this study over a 12-month follow-up period.

Methods

A retrospective analysis of commercial health insurance claims of MS relapses was conducted using Truven Health Analytics MarketScan® database. Patients with ≥ 2 MS relapse episodes between 2007 and 2012 were identified; the first relapse was treated with IVMP and following relapses were treated with Acthar, IVIG, or PMP. The first calendar date of the second treated relapse was the index date. Patients with continuous health plan enrollment for 6-months prior and 12-months post index date were included, with a subset who were able to be followed for 24 months. We estimated the healthcare resource use and costs (inpatient, outpatient, and pharmacy) separately for patients whose second relapse was treated with each treatment option and then compared Acthar to patients who received either IVIG or PMP. Multivariate linear regression models were constructed to adjust for measured baseline patient characteristics and prior resource use.

Results

A total of 439 MS patients had 12 months of continuous enrollment after their second MS exacerbation. 213 (49%) patients were treated with Acthar and 226 (51%) patients with IVIG/PMP for their second exacerbation. Of those, 228 had 24 months of continuous follow-up data, 96 (42%) Acthar and 132 (58%) IVIG/PMP. Patients who were treated with Acthar had a significantly lower number of hospitalizations (-0.4, 95% CI: -0.6 to -0.2) and outpatient visits (-17, 95% CI: -22 to -11) in the first 12 months, along with accompanying lower hospitalization (-$15,000) and outpatient (-$54,100) costs for those resources, with similar total costs at one year. In multivariate linear regression, the significant differences in reduced inpatient costs (-$11,600), outpatient encounters (-8.3, 95% CI: -14 to -2.1), and outpatient costs (-$47,700) remained. Additionally, total costs were still similar between the two groups in adjusted analyses. The findings of reduced outpatient services and costs and comparable total costs were consistent among the subgroups with 24 months of continuous follow-up data.

Conclusion

Patients with MS relapses that remain symptomatic despite initial treatment pose a challenge to clinicians and patients. In this analysis, we found that treating these relapses with ACTH may be associated with decreased resource use and similar costs compared to IVIG or PMP, thereby supporting the economic value of Acthar in MS relapse.

Background

- Multiple Sclerosis (MS) is an autoimmune disorder in which nerve cells in the brain and spinal cord are damaged, causing a wide range of neurological symptoms. As of 2013, more than 2.3 million people worldwide had been diagnosed with MS.[1]
- On average, annual direct costs for MS patients are about $24,000 higher compared to the non-MS population.[2] The major drivers of the increased costs in the MS population are expenses related to treating MS exacerbations (relapses). Medicare data showed that direct costs per year in patients who experienced relapses were around $17,000, while the costs during remission and period of stabilization were about $7,300 and $4,000 per year, respectively.[2]
- Relapses become more intense over time and the expense of treating them increases with severity.[3] Compared to a MS cohort with no relapses, those who experienced low/moderate severity relapses and high severity relapses had $8,269 and $24,180 higher annual incremental direct costs, respectively.[3]
  – Indirect costs additionally contributed $1,429 and $2,714 in the low/moderate severity relapse group and the high severity relapse group, respectively, compared to the no-relapse group.[3] Furthermore, MS diagnoses are associated with significantly reduced health-related quality of life, with MS patients having about ten fewer quality-adjusted life years (QALYs) compared to patients without MS.[4]
- Among pharmacological therapies for MS relapses, short courses of high-dose corticosteroids are often prescribed to reduce inflammation. Most commonly, these include intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIG), high-dose oral prednisone. Alternatively, Acthar and plasmapheresis (PMP) are also used.
- The aim of this study was to evaluate healthcare utilization, outcomes, and costs resulting from management of MS relapses with Acthar Gel compared to other available treatments among MS patients who experienced multiple relapses.

Methods

Study Population and Data Source

- Truven Health Analytics MarketScan® Commercial Claims and Encounters Databases.
  – Inpatient, outpatient, pharmacy claims, and insurance coverage data for patients across the U.S. who are covered by commercial insurance plans and Medicaid.
  – The inpatient and outpatient claims databases include procedure and visit level details from medical claims such as ICD-9-CM diagnosis and procedure codes, Current Procedural Terminology (CPT) medical procedure codes, dates of service, and variables describing financial expenditures.
  – The pharmacy claims database provided details including National Drug Codes (NDC), dates dispensed, quantity and days' supply, and payments made for each claim.
  – Eligibility and demographics file provided additional information about each subject such as age, gender, insurance plan type, employment status and classification, geographic location, and enrollment status by month.
- We limited our study to patients in the database who experienced at least two MS exacerbations between July 1, 2007 to December 31, 2012. Patients were followed for outcomes until December 31, 2013. We initially identified eligible patients with an MS diagnosis (ICD9-CM code 340.X) who had relapses that were treated with IVMP, the first-line treatment for MS relapse. Patients who were treated for subsequent relapses were eligible for the study.
  – The index date was the calendar date in which we observed a subsequent treated relapse at least 30 days after the initial relapse with the primary ICD9-CM diagnosis code for MS along with a claim for one of the relapse treatments: Acthar Gel, IVIG, or PMP.
  – We excluded patients who were not enrolled in their health plans continuously for 6 months prior and for 12 months after the index date.

Statistical Analysis

- We compared the use of Acthar versus PMP or IVIG.
  – Patients who took Acthar more than 30 days after their subsequent (index) exacerbation were excluded from these analyses, but patients in the Acthar group may have received other treatments (IVIG or PMP) in addition to Acthar within 30 days of the index exacerbation.
- We examined proportions and chi-square tests (for categorical variables) and means, standard deviations, and t-tests (for continuous variables) of factors that might have been related to health costs and outcomes and use of Acthar, including patient age, gender, type of health insurance plan, Deyo-Charlson co-morbidity index,[5,6] co-morbidity categories, geographic region, year of index relapse, and the number of outpatient visits, hospitalizations, and medications filled in the 6 months prior to index incident.
- We performed logistic regressions modeling receipt of Acthar against each variable to evaluate confounding; variables with p-values of ≤0.05 were considered significant confounders.
- Means, medians, ranges, and standard deviations of each healthcare utilization and cost among patients who received treatment with Acthar compared to patients who received PMP or IVIG.
- We performed unadjusted regressions to evaluate the association of Acthar with each outcome and also adjusted for patient variables that were significant in the preliminary regressions:
- For outcomes with count variables such as hospitalizations, length of hospital stay, admissions to an intensive care unit (ICU), emergency department visits, MS-related emergency department visits, outpatient services, rehabilitation and long-term care services, number of prescription medications filled, number of all healthcare services combined and number of relapses following the index relapse, we used generalized linear regression with a log link and specified the Poisson distribution to calculate relative rate (RR) ratios and 95% confidence intervals (95% CIs).
  – Outcomes related to hospitalizations (length of stay, ICU admissions, and readmissions) were only calculated among MS patients with at least 1 hospitalization.
  – Similarly, MS-related emergency department visits and long-term care stays were only evaluated among patients with at least 1 emergency department visit or one long-term care service, respectively.
- For the binary outcome of whether patients were readmitted to the hospital within 30 days of discharge, we used logistic regression to calculate odds ratios (ORs) and 95% CIs.
- For cost outcomes, we used generalized linear regressions with log links and specified the gamma distribution to calculate RR ratios and 95% CIs.
- Patients with 24-months of continuous eligibility were analyzed separately, measuring the same outcomes over a two-year period.
- SAS for Windows, Version 9.3 (SAS Institute, Inc., Cary, NC) was used for all analyses.
- This study was exempt from review by the University of Washington Institutional Review Board (IRB) through self-determination.

References

1. (MSIF) MSIF. Atlas of MS 2013: Mapping Multiple Sclerosis Around the World (pdf). Multiple Sclerosis International Federation, 2013. http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf.
2. Gilden DM, Kubisiak J, Zbrozek AS. The economic burden of Medicare-eligible patients by multiple sclerosis type. Value Health. Jan 2011;14(1):61-69.
3. Parise H, Laliberte F, Lefebvre P, et al. Direct and indirect cost burden associated with multiple sclerosis relapses: excess costs of persons with MS and their spouse caregivers. J Neurol Sci. Jul 15 2013;330(1-2):71-77.
4. Campbell JD, Ghushchyan V, Brett McQueen R, et al. Burden of multiple sclerosis on direct, indirect costs and quality of life: National US estimates. Mult Scler Relat Disord. Mar 2014;3(2):227-236.
5. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of clinical epidemiology. Jun 1992;45(6):613-619.
6. Austin SR, Wong YN, Uzzo RG, Beck JR, Egleston BL. Why Summary Comorbidity Measures Such As the Charlson Comorbidity Index and Elixhauser Score Work. Medical care. May 23 2013.
7. Ross AP, Ben-Zacharia A, Harris C, Smrtka J. Multiple sclerosis, relapses, and the mechanism of action of adrenocorticotropic hormone. Frontiers in neurology. 2013;4:21.
8. Berkovich R. Treatment of acute relapses in multiple sclerosis. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. Jan 2013;10(1):97-105.

Disclosure

This poster was presented at World Congress of Inflammation, August 8-12, 2015, Boston, MA

Results

Table 1. Characteristics of MS patients with 12-month outcomes who received Acthar compared to patients who received Plasmapheresis or IV immunoglobulin (IVIG) within 30 days of exacerbation

	Acthar Use[1] n=213 (49%)	PMP or IVIG n=226 (51%)	Chi-Square/t-test p-value[3]
Age (Mean (Range) ± SD)	43.6 (18-63) ± 10	43.0 (10-63) ± 11	0.57
Female	168 (79%)	184 (81%)	0.50
Type of Health Plan Comprehensive Exclusive/Preferred Provider Org. Health Maintenance Organization Point of Service Consumer Directed/High Deductible Missing	7 (3.5%) 136 (67%) 28 (14%) 18 (8.9%) 14 (6.9%) 10 (4.6%)	6 (3%) 150 (67%) 31 (14%) 25 (11%) 11 (5%) 3 (1%)	0.83
Charlson Comorbidity Index 0 1 2 3+	131 (62%) 42 (20%) 24 (11%) 16 (7.5%)	130 (58%) 49 (22%) 18 (8%) 29 (13%)	0.19
Comorbidity Groups Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Rheumatoid diseases Peptic ulcer disease Chronic Liver Disease Diabetes w/out complications Diabetes w/ complications Hemiplegia Renal disease Non-metastatic cancer Sequelae of chronic liver disease Metastatic Cancer AIDS	2 (0.9%) 2 (0.9%) 8 (3.7%) 18 (8.5%) 0 39 (18%) 12 (5.5%) 3 (1.4%) 1 (0.5%) 16 (7.3%) 2 (0.9%) 13 (6.1%) 3 (1.4%) 4 (1.9%) 0 1 (0.5%) 0	1 (0.4%) 2 (0.9%) 6 (2.7%) 27 (12%) 0 36 (16%) 17 (8%) 5 (2.2%) 1 (0.4%) 31 (14%) 5 (2.2%) 10 (4.4%) 5 (2.2%) 13 (5.8%) 1 (0.4%) 0 0	0.62 1.0 0.55 0.23 NA 0.51 0.38 0.72 1.0 **0.03** 0.45 0.43 0.73 0.05 1.0 0.49 NA
Geographic Region Northeast North Central South West Missing	47 (22%) 44 (20%) 90 (42%) 28 (13%) 4 (1.8%)	48 (22%) 44 (20%) 93 (43%) 30 (14%) 1 (0.4%)	0.10
Year of 2nd MS exacerbation 2007 2008 2009 2010 2011 2012	0 2 (0.9%) 14 (6.4%) 36 (16%) 76 (35%) 85 (40%)	14 (6%) 51 (23%) 55 (24%) 49 (22%) 36 (16%) 21 (9%)	**<0.0001**
Prior 6 months healthcare use (Mean (Range) ± SD) Outpatient visits Hospitalizations Medications	8.6 (0-45) ± 7.0 0.09 (0-3) ± 0.3 11.7 (0-60) ± 9.2	12 (0-36) ± 8 0.3 (0-3) ± 0.5 8.2 (0-78) ± 8.8	**<0.0001** **<0.0001** **<0.0001**

1 Patients who took Acthar may have received other treatments within 30 days of index exacerbation (n=8). 16 patients who used Acthar more than 30 days after index exacerbation deleted from these analyses.
2 By definition, patients who received PMP or IVIG could not have received Acthar.
3 Chi-square/t-test and odds ratios comparing patients who received Acthar to patients who received PMP or IVIG.

Table 2. Number and costs of unadjusted 12-month and 24-month outcomes among patients who received Acthar compared to patients who received Plasmapheresis or IV immunoglobulin (IVIG)

	12 Month Outcomes			24 Month Outcomes		
Outcome: Mean (Median) (Range) ± SD.	Acthar Use[1] n=213 (49%)	PMP or IVIG[2] n=226 (51%)	p-value	Acthar Use[1] n=96 (42%)	PMP or IVIG n=132 (58%)	p-value
All Healthcare Services	78.4 (69) (7-385) ± 49	82 (70) (9-300) ± 49	**<0.001**	157 (136) (14-528) ± 100	164 (141) (22-580) ± 94	**<0.0001**
Hospitalizations Length of Stay[4] Admissions to ICU[4] Readmissions 30 days[4]	0.2 (0) (0-4) ± 0.6 3.7 (3) (0-19) ± 3.6 0.1 (0) (0-1) ± 0.3 0.3 (0) (0-1) ± 0.4	0.6 (0) (0-9) ± 1.5 7.0 (4) (0-45) ± 8 0.2 (0) (0-2) ± 0.5 0.3 (0) (0-1) ± 0.4	**<0.0001** **<0.0001** 0.16 0.98	0.5 (0) (0-4) ± 1.0 4.4 (3) (1-11) ± 3.2 0.1 (0) (0-1) ± 0.4 0.4 (0) (0-3) ± 0.8	1.0 (0) (0-15) ± 2.1 5.7 (5) (0-34) ± 5.7 0.3 (0) (0-3) ± 0.6 0.7 (0) (0-10) ± 1.9	**<0.0001** **0.01** 0.36 0.79
ED visits MS-related ED visits	0.5 (0) (0-10) ± 1.2 0.8 (1) (0-6) ± 1.1	0.7 (0) (0-18) ± 1.8 0.9 (1) (0-6) ± 1.3	**0.02** 0.39	0.9 (0) (0-16) ± 2.2 1.2 (1) (0-10) ± 1.9	1.3 (0) (0-36) ± 3.7 1.1 (1) (0-10) ± 1.8	**0.01** 0.71
Outpatient services	31 (23) (2-366) ± 32	48 (41) 5-170) ± 29	**<0.0001**	56 (40) (6-255) ± 46	87 (76) (17-330) ± 53	**<0.0001**
Rehab and LTCF[5] Long-term care[6]	0.1 (0) (0-19) ± 1.3 0.1 (0) (0-19) ± 1.3	0.3 (0) (0-40) ± 2.8 0.1 (0) (0-8) ± 0.6	**<0.0001** 0.19	0.3 (0) (0-19) ± 2.1 0.3 (0) (0-19) ± 2.1	0.4 (0) (0-40) ± 3.5 0.04 (0) (0-4) ± 0.4	0.24 **<0.0001**
Prescription count	47 (39) (1-179) ± 33	33 (27) (0-230) ± 34	**<0.0001**	100 (81) (2-400) ± 74	75 (60) (0-430) ± 68	**<0.0001**
Inpatient Costs	3500 (0) (0-124,000) ± 14,000	18.8 (0) (0-490) ± 63	**0.001**	10,300 (0) (0-173,000) ± 26,000	27,700 (0) (0-677,000) ± 84,000	**0.01**
Outpatient Costs Total Outpatient Costs (minus J-code Costs)	30,300 (10,200) (300 - 2,500,000) ± 175,000 30,000 (10,200) (300-2,550,000) ± 175000	84,400 (61,000) (2000-886,000) ± 89,000 84,400 (61,000) (2000-886,000) ± 89,000	**<0.0001** **<0.0001**	26,600 (13,200) (1300-175,000) ± 32,300 2800 (3300) (300-4500) ± 2000	148,000 (105,000) (7700-1,835,000) ± 185000 11,800 (1700) (200-60,000) ± 23,800	**<0.0001** 0.12
Medication Costs Total Medication Costs (minus Acthar costs)	87,200 (78600) (0-440,000) ± 55,000 30,800 (30400) (0-88,000) ± 21,000	12,300 (4000) (0-111,000) ± 18,000 12,300 (4000) (0-111,000) ± 18,000	**<0.0001** **<0.0001**	138,000 (122,000) (0-563,000 ± 92,000 65,000 (63,000) (0-181,000) ± 43,000	33,000 (13,000) (0-234,000 ± 42,000 33,000 (13,000) (0-234,000) ± 42,000	**<0.0001** **0.002**
Total Costs Total Cost of Services minus Acthar costs	121,000 (94,400) (3400-2,580,000) ± 180,000 64,000 (50,600) (1200-2,550,000) ± 174,000	115,000 (86,000) (4000-940,000) ± 110,000 115,000 (86,000) (4000-940,000) ± 110,000	0.49 **<0.0001**	175,000 (147,000) (30,000-689,000) ± 107,000 102,000 (95,000) (3000-385,000) ± 62,000	208,000 (164,000) (7700-2,0210,000) ± 212,000 208,000 (164,000) (7700-2,0210,000) ± 212,000	0.06 **<0.0001**

1 Patients who took Acthar may have received other treatments within 30 days of index exacerbation (n=11). 16 patients who used Acthar > 30 days after index exacerbation deleted from analyses.
2 By definition, patients who received PMP or IVIG could not have received Acthar.
3 For count outcomes (all health care services, hospitalizations, mean LOS, ICU admissions, emergency department visits, MS-related ED visits, outpatient services, rehab & long-term services, prescription medication count, & relapses), link=log & dist=Poisson models used. For binary outcome (readmissions within 30 days yes/no), proc logistic used. For cost outcomes, link=log & dist=gamma models used.
4 Length of stay, admissions to ICU, and readmissions within 30 days calculated only among patients with at least 1 hospitalization.
5 Rehab= Rehabilitation; LTCF = Long term care facility. This includes rehab facilities (inpatient and outpatient), skilled nursing facilities, inpatient long-term care, nursing facilities, custodial care facilities.
6 This includes ONLY inpatient and outpatient long-term care facilities and is a subset of the line above.

Table 3. Adjusted 12-month and 24-month outcomes among patients who received Acthar compared to patients who received Plasmapheresis or intravenous immunoglobulin (IVIG)

	12-Month Outcomes Compared to PMP or IVIG: Relative Rate/Odds Ratio (95% CI)[1]	p-value	24-Month Outcome Compared to PMP or IVIG Relative Rate/Odds Ratio (95% CI)[1]	p-value
All Health care Services	0.96 (0.93-0.99)	**0.005**	0.95 (0.93-0.98)	**0.001**
Hospitalizations Length of Stay[2] Admissions to ICU[2] Readmissions 30 days[2]	0.6 (0.4-0.9) 0.4 (0.3-0.6) Model did not converge 1.5 (0.3-8.2)	**0.01** **<0.0001** -- 0.66	0.5 (0.3-0.8) 0.8 (0.6-1.1) Model did not converge 0.9 (0.1-5.4)	**0.004** 0.11 -- 0.89
ED visits MS-related ED visits	0.8 (0.6-1.1) 0.9 (0.5-1.4)	0.14 0.53	0.7 (0.5-1.0) Model did not converge	0.06 --
Outpatient services	0.76 (0.73-0.79)	**<0.0001**	0.71 (0.68-0.74)	**<0.0001**
All Rehab & long-term care facilities services[3] Long-term care[4]	0.2 (0.1-0.4) Model did not converge	**<0.0001** --	Model did not converge Model did not converge	-- --
Prescription count	1.21 (1.16-1.26)	**<0.0001**	1.16 (1.12-1.20)	**<0.0001**
Inpatient Costs	0.4 (0.2-0.9)	**0.02**	0.7 (0.3-1.3)	0.25
Outpatient Costs Total Outpatient Costs minus J-code Costs	0.24 (0.19-0.31) 0.24 (0.19-0.31)	**<0.0001** **<0.0001**	0.17 (0.13-0.24) Model did not converge	**<0.0001** --
Medication Costs Total Medication Costs minus Acthar costs	4.5 (3.6-5.7) 1.5 (1.1-2.0)	**<0.0001** **0.006**	3.2 (2.3-4.4) 1.4 (0.9-2.0)	**<0.0001** 0.11
Total Costs Total Cost of Services minus Acthar costs	1.0 (0.8-1.1) 0.5 (0.4-0.6)	0.74 **<0.0001**	0.9 (0.7-1.1) 0.5 (0.4-0.6)	0.19 **<0.0001**

1 Adjusted for number of relapses prior to index date, comorbid diabetes without complications, year of index exacerbation, and number of outpatient visits, hospitalizations, and medications in the 6 months prior to the index exacerbation. For count outcomes (all health care services, hospitalizations, mean LOS, ICU admissions, emergency department visits, MS-related ED visits, outpatient services, rehab & long-term services, prescription medication count, and relapses), link=log and dist=Poisson models used. For binary outcome (readmissions within 30 days yes/no), proc logistic used. For cost outcomes, link=log and dist=gamma models used.
2 Length of stay, admissions to ICU, and readmissions within 30 days calculated only among patients with at least 1 hospitalization.
3 This includes rehab facilities (inpatient and outpatient), skilled nursing facilities, inpatient long-term care, nursing facilities, custodial care facilities.
4 This includes ONLY inpatient and outpatient long-term care facilities and is a subset of the line above.

Discussion

- Acthar recipients for MS exacerbations utilize less health services and had reduced inpatient, outpatient, and long-term care costs over the subsequent 12 months and 24 months compared to recipients of plasmapheresis or IVIG. Total health care costs were similar between groups.

Limitations

- We cannot be certain that the differences we observed between patients who did and did not receive Acthar could not be explained by confounding factors. We attempted to correct for this by adjusting our models for potentially confounding variables (diabetes without complications and non-metastatic cancer), but unmeasured factors might play a role in the associations that we reported.
- The population of patients in the MarketScan® databases is not randomly sampled and some populations, such as patients insured by small employers were not represented in this study population. Therefore, these results may not be generalizable across all MS patients in the U.S.

Conclusion

- Compared to patients using PMP or IVIG, patients using Acthar had fewer outpatient visits and hospitalizations, which resulted in lower costs in those categories as well.
- Acthar may be a useful treatment option for MS patients experiencing multiple relapses.

Economic Consequences of Early versus Late use of Adrenocorticotropic Hormone Therapy in Infantile Spasms

Ryan N. Hansen, PharmD, PhD[1]; Laura S. Gold, PhD[1]; Patricia Schepman, PharmD, PhD[3], John Niewoehner, PharmD[2]; Michael Philbin, PharmD, MBA[2]; Kavitha Damal, PhD[2].
[1]*Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy, University of Washington, Seattle, WA;* [2]*Mallinckrodt Pharmaceuticals, St. Louis, MO;* [3] *Formerly at Mallinckrodt Pharmaceuticals, St. Louis, MO*

Abstract

Background

Infantile spasms (IS) typically occur within the first year of life. Children with IS frequently experience spasms, hypsarrhythmia and psychomotor retardation. H.P. Acthar® Gel is an adrenocorticotropic hormone (ACTH) analogue that is FDA approved for the treatment of IS.[1] Evidence-based guidelines recommend the use of ACTH as first-line therapy for IS.[2-4] Long-term prognosis of IS patients, specifically neurodevelopmental outcomes, is relatively poor. Prompt diagnosis and treatment may reduce healthcare utilization and costs.

Objective

We compared the economic consequences of initiating ACTH early (within 30 days of IS diagnosis) with that of late ACTH treatment (> 30 days after diagnosis).

Methods

All patients < 2 years old with an IS diagnosis who received ACTH between 2007 and 2012 were identified from the Truven Health Analytics MarketScan® commercial and Medicaid claims and encounters databases. Based on the first calendar date of IS diagnosis (index date), patients were classified into two groups: early users (received ACTH within 30 days of the index date) and late users (received ACTH >30 days of the index date). Patients with continuous health plan enrollment for 3-months prior and 12-months post index date were included in this retrospective analysis. We estimated and compared the healthcare resource use and costs (inpatient, outpatient, and pharmacy) separately for patients in the two groups. Multivariate regression models were constructed to adjust for gender and prior hospitalization.

Results

We identified a total of 259 IS patients who met our study eligibility criteria. 197 (76%) patients used ACTH early and 62 (24%) patients were late users of ACTH. Over the one-year follow-up from IS diagnosis, early users had 16% fewer outpatient visits (95% CI: -13% to -19%) and 15% less overall healthcare resource utilization (95% CI: -13% to -18%) when compared to late ACTH users. Unadjusted 12-month total outpatient costs (excluding the costs of administering ACTH) for early users were 30% lower ($23,200 for early users as compared to $33,500 for late users; 95% CI: -10% to -50%) as were the total medication costs excluding cost of ACTH 50% reduced (95% CI: -20% to -70%). After adjusting for gender and prior hospitalizations, the relative rate ratio of outpatient visits (0.89; 95% CI: 0.85 to 0.92), overall healthcare resource utilization (0.91; 95% CI: 0.88 to 0.94) and total medication costs (excluding ACTH costs) (0.5; 95% CI: 0.3 to 0.8) were statistically significantly lower in early ACTH users than late users.

Conclusion

In this analysis, we found that the economic consequences of treating patients with ACTH within 30 days of IS diagnosis may be associated with decreases in overall healthcare resource use, outpatient visits and total medication costs.

Background

- Infantile Spasms (IS; West syndrome) is an uncommon but often devastating form of epilepsy that typically occurs in the first year of life.[1]
- Although spasms usually resolve by age 5, ineffective treatment is associated with poor outcomes such as refractory epilepsy, mental retardation, and autistic spectrum disorders.[1,2] A systematic review estimated that 84% of infants diagnosed with IS went on to experience developmental delays of some kind.[3]
- The first-line therapies for IS are hormonal therapies such as repository corticotropin injection (ACTH; H.P. Acthar Gel) and, in non-U.S. countries, vigabatrin.[2]
  - Following treatment, infants typically undergo electroencephalograms to evaluate treatment effectiveness and, if indicated, treatments are modified.[2]
  - Subsequent treatments that have been found to be effective in some instances include high-dose oral prednisolone, surgery (but only for children with surgical lesions), or the ketogenic diet, though the efficacy of this has not been shown with controlled trials for IS patients.[2]
- H.P. Acthar Gel (repository corticotropin injection) is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.[8]
- Although analysis of health care resource utilization in patients with convulsive disorders is the starting point for economic assessment of the medical burden of these conditions, little research has focused on the nature and components of patients' needs for care.
- The purpose of this study was to compare health outcomes and costs resulting from early (within 30 days of diagnosis) management of IS with Acthar Gel, versus later (more than 30 days after diagnosis) use of this drug.

Methods

Study Population and Data Source

- Truven Health Analytics MarketScan® Commercial Claims and Encounters and Medicaid Databases.
  - Inpatient, outpatient, pharmacy claims, and insurance coverage data for patients across the U.S. who are covered by commercial insurance plans and Medicaid.
  - The inpatient and outpatient claims databases include procedure and visit level details from medical claims such as ICD-9-CM diagnosis and procedure codes, Current Procedural Terminology (CPT) medical procedure codes, dates of service, and variables describing financial expenditures.
  - The pharmacy claims database provided details including National Drug Codes (NDC), dates dispensed, quantity and days' supply, and payments made for each claim.
  - Eligibility and demographics file provided additional information about each subject such as age, gender, insurance plan type, employment status and classification, geographic location, and enrollment status by month.
- We included all patients in the MarketScan® Research Databases who received treatment for Infantile Spasms (ICD9-CM diagnosis code: 345.60) between April 1, 2007 and December 31, 2012 who were 2 years old or younger at the time of the IS diagnosis.
  - We excluded patients who were not enrolled in their health plans continuously for 90 days prior and 12 months after the index date and patients with tuberous sclerosis (ICD9-CM diagnosis code 759.5).
  - We classified patients in our study cohort who had outpatient prescriptions or a procedure codes indicating the use of Acthar (National Drug Codes: 63004-7731-01, 63004-8710-01; Current Procedural Terminology code: J0800) into those who took Acthar early (within 30 days of the index IS incident) and those who took Acthar late (more than 30 days after the index IS incident).
  - Patients who had prescriptions for early *and* late Acthar were included in the early Acthar group.

Statistical Analysis

- We calculated proportions and chi-square tests (for categorical variables) or means, standard deviations, and t-tests (for continuous variables) of factors that might have been related to health costs and outcomes and early use of Acthar, including:
  - Patient age,
  - gender,
  - type of health insurance plan (both types of private plans and Medicaid versus non-Medicaid),
  - geographic region (region data were not available for patients with Medicaid), year of IS diagnosis, and
  - the number of outpatient visits, hospitalizations, and medications filled in the 90 days prior to index incident.
- We performed logistic regressions modeling early receipt of Acthar against each variable to evaluate confounding; variables with p-values of ≤0.05 were considered significant confounders.
- Means, medians, ranges, and standard deviations of each healthcare utilization and cost among patients who received early treatment with Acthar were compared to patients who received late treatment with Acthar.
- We performed unadjusted regressions to evaluate the associations of early vs. late Acthar use and also adjusted for patient variables that were significantly associated with early use of Acthar:
- For outcomes with count variables such as hospitalizations, length of hospital stay, admissions to an intensive care unit (ICU), emergency department visits, IS-related emergency department visits, outpatient visits, counts of prescription medications filled, and counts of all healthcare services combined, we used generalized linear regression with log links and specified the Poisson distribution to calculate relative rate (RR) ratios and 95% confidence intervals (95% CIs).
  - Outcomes related to hospitalizations (length of stay, ICU admissions, and readmissions) were only calculated among IS patients with at least 1 hospitalization.
  - Similarly, IS-related emergency department visits were only evaluated among patients with at least 1 emergency department visit.
- For the binary outcome of whether patients were readmitted to the hospital within 30 days of discharge, we used logistic regression to calculate odds ratios (ORs) and 95% CIs.
- For cost outcomes, we used generalized linear regressions with log links and specified the gamma distribution to calculate RR ratios and 95% CIs.
- For outpatient and medication costs, we also calculated the costs subtracting the costs of the Acthar prescription or its administration.
- SAS for Windows, Version 9.3 (SAS Institute, Inc., Cary, NC) was used for all analyses.
- This study was exempt from review by the University of Washington Institutional Review Board (IRB) through self-determination.

References

1. *Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. Oct 2010;51(10):2175-2189.*
2. *Wheless JW, Gibson PA, Rosbeck KL, et al. Infantile spasms (West syndrome): update and resources for pediatricians and providers to share with parents. BMC Pediatr. 2012;12:108.*
3. *Hrachovy RA, Frost JD, Jr. Infantile epileptic encephalopathy with hypsarrhythmia (infantile spasms/West syndrome). Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. Nov-Dec 2003;20(6):408-425.*
4. *Gettig J, Cummings JP, Matuszewski K. H.p. Acthar gel and cosyntropin review: clinical and financial implications. P & T : a peer-reviewed journal for formulary management. May 2009;34(5):250-257.*
5. *O'Callaghan FJ, Lux AL, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. Epilepsia. Jul 2011;52(7):1359-1364.*
6. *Rener-Primec Z, Lozar-Krivec J, Krivec U, Neubauer D. Head growth in infants with infantile spasms may be temporarily reduced. Pediatr Neurol. Sep 2006;35(3):197-203.*
7. *Goh S, Kwiatkowski DJ, Dorer DJ, Thiele EA. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. Neurology. Jul 26 2005;65(2):235-238.*
8. *H.P. Acthar® Gel Package Insert, Mallinckrodt Pharmaceuticals, Hazelwood, MO.*

Disclosure

PRESENTED AT THE 13th WORLD CONGRESS ON INFLAMMATION, AUGUST 8-12, 2015, BOSTON, MASSACHUSETTES

Results

Table 1. Characteristics of infantile spasm patients using Acthar within 30 days of index diagnosis compared to patients using Acthar more than 30 days after diagnosis.

	Early Acthar Use* n=197 (76%)	Late Acthar Use* n=62 (24%)	p-value**	Odds Ratio (95% CI)**
Age in years (mean (range) ± SD)	0.61 (0-1) ± 0.49	0.65 (0-1) ± 0.48	0.66	0.9 (0.5-1.6)
Age 0 - <1	76 (36%)	22 (32%)		Referent
Age 1 - <2	121 (58%)	40 (58%)	0.66	0.9 (0.5-1.6)
Female	76 (39%)	34 (55%)	**0.02**	**0.5 (0.3-0.9)**
Non-Medicaid	158 (80%)	50 (81%)	0.94	Referent
Medicaid	39 (20%)	12 (19%)		1.0 (0.5-2.1)
Type of Health Plan				
Comprehensive	19 (10%)	9 (15%)		Referent
Preferred Provider Org.	94 (48%)	33 (54%)		1.4 (0.6-3.3)
HMO	50 (25%)	9 (15%)	0.35	2.6 (0.9-7.6)
Point of Service	19 (10%)	7 (11%)		1.3 (0.4-4.2)
High Deductible	15 (7.6%)	3 (4.9%)		2.4 (0.9-7.6)
Missing	0	1 (1%)		
Geographic Region				
Northeast	27 (13%)	9 (15%)		Referent
North Central	48 (26%)	13 (21%)	0.71	1.2 (0.5-3.3)
South	52 (24%)	16 (26%)		1.1 (0.4-2.8)
West	26 (14%)	12 (19%)		0.7 (0.3-2.0)
Missing***	44 (22%)	12 (19%)		
Year of IS incident				
2007	31 (16%)	7 (11%)		Referent
2008	37 (19%)	21 (34%)		0.4 (0.2-1.1)
2009	34 (17%)	8 (13%)	0.24	1.0 (0.3-3.0)
2010	36 (18%)	11 (18%)		0.7 (0.3-2.1)
2011	31 (16%)	9 (15%)		0.8 (0.3-2.4)
2012	28 (14%)	6 (10%)		1.1 (0.3-3.5)
Days -90 to -1 (mean (range) ± SD)				
Outpatient visits	10.1 (0-54) ± 9.5	12.3 ± 9.4 (1-38)	0.10	0.98 (0.95-1.01)
Hospital Admissions	0.2 (0-2) ± 0.5	0.6 ± 1.0 (0-4)	**<0.0001**	**0.5 (0.3-0.7)**
Medications	3.5 ± 4.8 (0-31)	3.9 ± 4.4 (0-19)	0.54	0.98 (0.93-1.04)

**Patients could have had both early AND late Acthar (n=63).*
***p-values and odds ratios show odds of early Acthar e.g., a female was 50% as likely to have taken early Acthar as a male.*
****Region data missing from Medicaid.*

Table 2. Unadjusted 12-month outcomes among patients who received Acthar within 30 days of infantile spasms diagnosis compared to those who received Acthar more than 30 days after diagnosis.

Variable (mean (median) ± standard deviation (range) [in US $$]	Early Acthar Use* n=197 (76%)	Late Acthar Use* n=62 (24%)	p-value	Relative Rate/Odds Ratio (95% CI)**
Hospitalizations	2.2 (2.0) ± 1.9 (0-10)	2.4 (2.0) ± 2.0 (0-10)	0.60	1.0 (0.8-1.1)
Mean LOS***	4.1 (3.0) ± 4.2 (0.8-43)	4.3 (3.0) ± 4.9 (0-28)	0.11	1.0 (0.8-1.1)
ICU admissions***	0.3 (0) ± 0.7 (0-4)	0.5 (0) ± 1.5 (0-10)	**0.04**	**0.6 (0.4-0.9)**
Readmissions within 30 days***	0.3 (0) ± 0.5 (0-1)	0.3 (0) ± 0.4 (0-1)	0.22	1.5 (0.8-3.0)
Emergency department visits	1.0 (0) ± 1.6 (0-10)	1.1 (1.0) ± 1.5 (0-6)	0.68	0.9 (0.7-1.2)
IS-related ED visits* **	0.2 (0) ± 0.5 (0-2)	0.2 (0) ± 0.5 (0-2)	0.85	1.1 (0.5-2.4)
Outpatient visits	61 (49) ± 42 (10-260)	73 (64) ± 42 (10-168)	**<0.0001**	**0.84 (0.81-0.87)**
Prescription medication count	30 (27) ± 22 (0-130)	36 (26) ± 23 (6-110)	**<0.0001**	**0.85 (0.81-0.90)**
All Health care Services	94 (82) ± 57 (14-330)	110 (110) ± 59 (29-250)	**<0.0001**	**0.85 (0.82-0.87)**
Total Hospitalization Costs	71,300 (21,200) ± 168,000 (0-1,360,000)	75,100 (16,900) ± 151,000 (0-723,000)	0.75	0.9 (0.6-1.4)
Total Outpatient Costs ($)	37,700 (17,200) ± 57,700 (0-425,000)	44,100 (21,800) ± 69,500 (1200-472,000)	0.33	0.9 (0.6-1.2)
Total Outpatient Costs minus J-code Costs	23,200 (15,200) ± 25,900 (0-182,000)	33,500 (19,400) ± 51,800 (1200-400,000)	**0.005**	**0.7 (0.5-0.9)**
Total Medication Costs	92,200 (84,200) ± 81,000 (0-495,000)	86,900 (79,800) ± 76,600 (0-290,000)	0.86	1.0 (0.7-1.5)
Total Medication Costs minus Acthar costs	4900 (1500) ± 10,400 (0-92,000)	9100 (3000) ± 13,400 (0-61,000)	**0.002**	**0.5 (0.3-0.8)**
Total Cost of Services	201,000 (148,000) ± 201,000 (7400-1,582,000)	206,000 (145,000) ± 199,000 (5400-952,500)	0.85	1.0 (0.8-1.2)
Total Cost of Services minus Acthar costs	99,300 (42,500) ± 178,000 (3200-1,460,000)	118,000 (54,500) ± 169,000 (5400-808,000)	0.29	0.8 (0.6-1.2)

** Patients could have had both early AND late Acthar (n=63) and those subjects were counted only in the early Acthar cohort.*
*** For count outcomes (Hospitalizations, Mean LOS, ICU admissions, Emergency department visits, IS-related ED visits, outpatient visits, prescription medication count, and all health services), link=log and dist=Poisson models used. For binary outcome (readmissions within 30 days yes/no), proc logistic used. For cost outcomes, link=log and dist=gamma models used.*
**** Mean length of stay, number of ICU admissions, and whether patients had any 30-day readmissions calculated only among patients with at least one hospitalization; IS-related ED visits calculated only among people with at least 1 ED visit.*

Table 3. Multivariate regression estimates among patients who received Acthar within 30 days of infantile spasms diagnosis compared to those who received Acthar more than 30 days after diagnosis

	Relative Rate/Odds Ratio (95% CI)*	p-value
Hospitalizations	1.0 (0.9-1.3)	0.70
Mean LOS**	1.0 (0.8-1.1)	0.71
ICU admissions**	0.9 (0.5-1.7)	0.84
Readmissions within 30 days**	1.7 (0.8-3.6)	0.14
Emergency department visits	1.1 (0.8-1.5)	0.43
IS-related ED visits**	1.5 (0.6-3.9)	0.39
Outpatient visits	**0.89 (0.85-0.92)**	**<0.0001**
Prescription medication count	0.95 (0.91-1.00)	0.08
All Health care Services	**0.91 (0.88-0.94)**	**<0.0001**
Total Hospitalization Costs	0.9 (0.6-1.4)	0.70
Total Outpatient Costs	1.0 (0.7-1.3)	0.85
Total Outpatient Costs minus J-code Costs	0.9 (0.7-1.2)	0.40
Total Medication Costs	1.0 (0.7-1.5)	0.84
Total Medication Costs minus Acthar costs	**0.5 (0.3-0.8)**	**0.005**
Total Cost of Services	1.0 (0.8-1.3)	0.98
Total Cost of Services minus Acthar costs	0.9 (0.6-1.3)	0.57

** Adjusted for gender and total hospitalizations in prior three months. For count outcomes (Hospitalizations, Mean LOS, ICU admissions, Emergency department visits, IS-related ED visits, outpatient visits, prescription medication count, and all health services), link=log and dist=Poisson models used. For binary outcome (readmissions within 30 days yes/no), proc logistic used. For cost outcomes, link=log and dist=gamma models used.*
***Mean length of stay (LOS), ICU admissions and readmissions within 30 days calculated only among patients with at least one hospitalization; IS-related ED visits calculated only among people with at least 1 ED visit.*

Discussion

- The majority of the infantile spasms patients in our cohort received Acthar within 30 days of their IS diagnoses
- Relative to patients who received Acthar more than 30 days after diagnosis, this group tended to have less health care utilization and lower costs.
  - Patients who received Acthar early had fewer outpatient visits, less use of health care services overall, and reduced spending on medications once Acthar costs were subtracted.

Limitations

- We cannot be certain that the differences we observed between patients who received Acthar early versus later could not be explained by confounding factors. We attempted to correct for this by adjusting our models for potentially confounding variables, but unmeasured factors might play a role in the associations that we reported.
- The population of patients in the MarketScan® databases is not randomly sampled and some populations, such as patients insured by small employers were not represented in this study population. Therefore, these results may not be generalizable across all IS patients in the U.S.

Conclusion

- We determined that earlier use of Acthar (compared to later use) to treat infantile spasms was associated with:
  - ✓ Reduced healthcare utilization
  - ✓ Reduced medication costs after accounting for the cost of Acthar
- Future analyses should focus on:
  - ✓ Identifying a larger cohort of IS patients to reduce uncertainty
  - ✓ Examining the economic outcomes among patients who receive Acthar compared to other IS treatments
  - ✓ Evaluating the long term outcomes of Acthar treatment in IS patients

Healthcare Resource Utilization and Work Loss in Dermatomyositis and Polymyositis Patients in a Privately-Insured Population in the US

J. Bradford Rice, PhD[1]; Alan White, PhD[1]; Andrea Lopez, MSc[1]; Philip Galebach, BA[1]; Patricia Schepman, PhD, MSc, PharmD[2]*; Breanna Popelar, PharmD, MS[3]; Michael Philbin, PharmD, MBA[2]

[1] Analysis Group, Inc., Boston, MA, USA [2] Mallinckrodt Pharmaceuticals, St. Louis, MO, USA [3] Xcenda, Palm Harbor, FL, USA
*Affiliated with Mallinckrodt Pharmaceuticals at the time this study was conducted.

Mallinckrodt Pharmaceuticals

BACKGROUND

- Dermatomyositis and polymyositis (DM/PM) are systemic autoimmune inflammatory myopathies characterized by chronic muscle inflammation and muscle weakness[1]
- The estimated incidence of DM/PM is 2 cases per 100,000 persons in the United States[2]; prevalence may be as high as 22 cases per 100,000 persons[3]
- Patients with DM/PM have a reduced quality of life and are at an increased risk for a number of comorbidities[4–8]
  - Studies have estimated that DM/PM patients have up to 7-fold increased risk of developing cancer compared with the general population[6,7]
  - DM/PM patients are also at an increased risk of heart attack and stroke and have a high prevalence of interstitial lung disease[5,8]
- The overall mortality ratio in DM/PM patients is three-fold higher compared with the general population, with cancer, lung, and cardiac complications and infections being the most common causes of death[9]
- While studies have assessed the incidence and prevalence of DM/PM, no study has estimated the burden of the disease in terms of healthcare resource utilization (HCRU) or medically-related work loss incurred by patients

OBJECTIVE

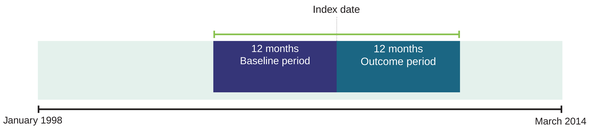
- To provide a robust, current estimate of the annual HCRU and work loss associated with DM/PM in the United States

METHODS

Data

- This study used OptumHealth Reporting and Insights, a de-identified privately-insured administrative claims database with claims spanning from January 1, 1998 to March 31, 2014
- This database includes claims for over 18.5 million beneficiaries (including employees, spouses, dependents, and retirees) with commercial insurance from over 80 large self-insured Fortune 500 companies with locations across the US
- The database contains information regarding patient age, gender, enrollment history, medical diagnoses, procedures performed, dates and place of service, and payment amounts as well as prescription drug claims for all beneficiaries; comprehensive cost data is only available for those under age 65 (non-Medicare)
- Measures of work loss (i.e., short- and long-term disability claims) were available for employees (i.e., primary policy holders) in 42 of the companies

Study Periods



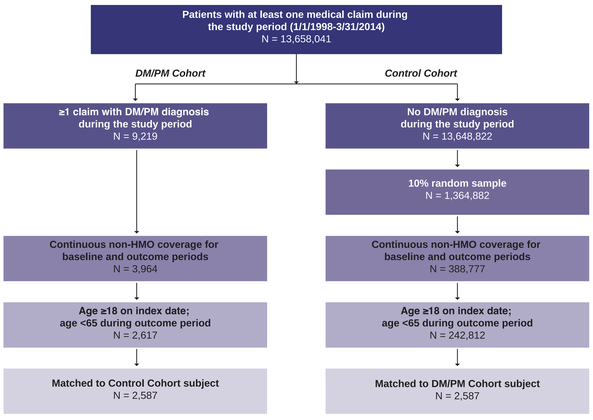
Study period
Patients with a DM/PM diagnosis between January 1, 1998 and March 31, 2014 ("study period") were identified, with the date of each patient's earliest DM/PM diagnosis defined as the "index date" (the index date for the control group was defined as a randomly selected medical claim occurring during the study period)

Baseline period
Patient characteristics in the 12 months prior to the index date ("baseline period") were assessed to create DM/PM and control cohorts with comparable characteristics (using propensity score matching)

Outcome period
Medical resource utilization and work loss in the 12 months following the index date ("outcome period") were compared in the matched DM/PM and control cohorts

Sample Selection

Figure 1. Selection of DM/PM patients and non-DM/PM controls



Propensity Score Matching

- To account for underlying differences between the two cohorts, DM/PM patients were matched one-to-one to non-DM/PM controls using a "greedy" matching methodology[10] based on the likelihood of having been diagnosed with DM/PM determined by propensity scores (±1/8 standard deviation)
- Propensity scores were calculated for patients using a multivariate logistic regression with the following covariates measured at baseline: age, gender, region, year of index date, Charlson Comorbidity Index, comorbid conditions common among DM/PM patients (i.e., rheumatic disease, rheumatoid arthritis, systemic lupus erythematosus, chronic obstructive pulmonary disease, diabetes without chronic complication, mild liver disease, any malignancy except neoplasm of the skin), number of medical visits (emergency department, inpatient, outpatient, other [e.g., home health, extended care, hospice], rheumatologist, neurologist, physical therapy), number of prescriptions filled, and total costs (medical costs, prescription drug costs)
- Matched pairs were also required to have the same availability of work loss data

Study Measures

- Baseline period evaluation
  - Demographic and clinical characteristics as well as number and cost of medical visits and prescriptions filled during the 12-month baseline period were summarized for the DM/PM and non-DM/PM control cohorts
  - Baseline characteristics of the two cohorts were evaluated pre- and post-match to assess quality of match and identify any enduring differences
- Outcome period evaluation
  - *All-cause healthcare resource use*
    - Number of medical visits, overall as well as categorized by place of service: inpatient, outpatient/physician office, emergency department (ED), other (e.g., home health, extended care, hospice) as well as select visits to medical specialists (i.e., neurologists, rheumatologists, physical therapists)
    - Number and type of prescriptions filled
  - *DM/PM-related healthcare resource use*
    - Utilization was considered "DM/PM-related" if a DM/PM diagnosis was recorded on the claim
  - *Work loss*
    - Work loss was estimated for a subgroup of patients with disability and employment information available
    - Number of days associated with short- and long-term disability were obtained directly from the database
    - Number of days associated with medically-related absenteeism was estimated using medical claims occurring during the workweek; each hospitalization day or ED visit accounted for a full day of absenteeism, all other visits accounted for half a day of absenteeism

Statistical Analyses

- Pre-match: Types and frequency of HCRU and work loss were compared using Wilcoxon rank-sum tests for continuous variables and chi-squared tests for categorical variables
- Post-match: Types and frequency of HCRU and work loss were compared using Wilcoxon signed-rank tests for continuous variables and McNemar tests for categorical variables

RESULTS

Baseline Characteristics

- A total of 2,617 DM/PM patients and 242,812 potential non-DM/PM control patients met inclusion criteria; among these, 2,587 DM/PM patients were matched to 2,587 non-DM/PM controls **(Figure 1)**
- Prior to matching, DM/PM patients were statistically different from the non-DM/PM control population on every measure examined during the baseline period (**Table 1**)
  - DM/PM patients were older (49.5 vs. 43.4 years) and had statistically significantly higher rates of rheumatic diseases such as rheumatoid arthritis (9.9% vs. 0.6%) and systemic lupus erythematosus (8.1% vs. 0.2%) compared with non-DM/PM controls during the baseline period
  - DM/PM patients had more inpatient admissions (+136.4%), ED visits (+75.0%), and outpatient/physician office visits (+106.0%) in the baseline period
  - Baseline healthcare costs among DM/PM patients were approximately 2.5 times those of the potential control population ($14,857 vs. $5,781)
- After matching DM/PM patients with comparable controls, the 2,587 pairs of DM/PM and control patients had similar baseline demographics and comorbidities (**Table 1**)
  - In particular, the matched DM/PM and control groups had comparable HCRU during the baseline period (23.6 vs. 23.7 medical visits, 26.0 vs. 26.4 prescriptions filled)
  - However, due to non-parametric tests performed, some characteristics did remain statistically significant, though not clinically meaningful

RESULTS (CONT.)

Baseline Characteristics (cont.)

Differences between the DM/PM and control populations were largely eliminated after matching

Table 1. Patient characteristics, resource utilization, and healthcare costs during the baseline period

	Pre-Match		Post-Match	
	DM/PM Cohort (N = 2,617)	Control Cohort (N = 242,812)	DM/PM Cohort (N = 2,587)	Control Cohort (N = 2,587)
Age (years), mean	49.5	43.4*	49.4	50.6*
Male, %	35.4%	48.4%*	35.6%	36.2%
Charlson Comorbidity Index, mean	1.0	0.3*	1.0	1.0
Selected comorbid conditions, %				
Rheumatic disease	22.3%	1.0%*	21.5%	20.2%*
Rheumatoid arthritis	9.9%	0.6%*	9.5%	10.5%
Systemic lupus erythematosus	8.1%	0.2%*	7.7%	6.2%*
Chronic obstructive pulmonary disease	15.1%	6.3%*	14.7%	16.0%
Diabetes without chronic complications	11.7%	5.5%*	11.5%	12.6%
Mild liver disease	5.8%	1.5%*	5.7%	6.1%
Any malignancy except neoplasm of skin	5.9%	2.8%*	5.8%	6.5%
Number of prescriptions filled, mean	26.6	11.7*	26.0	26.4
Number of medical visits, mean	24.1	11.2*	23.6	23.7*
Inpatient admissions	2.6	1.1*	2.5	2.4*
ED visits	0.7	0.4*	0.7	0.7
Outpatient visits	17.3	8.4*	17.0	17.2*
Other visits (e.g., home health, extended care)	3.5	1.4*	3.4	3.4*
Healthcare costs†, mean	$14,857	$5,781*	$14,622	$14,276

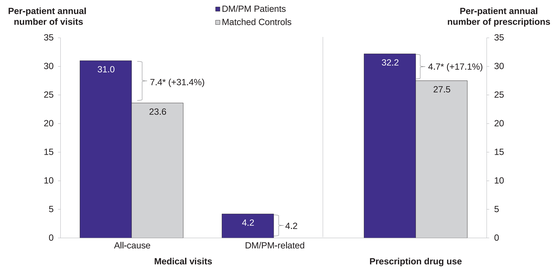
* Statistically different from the DM/PM cohort at the 0.05 significance level.
† Costs inflated to 2013 USD using the medical care component of the Consumer Price Index.

Healthcare Resource Use During the Outcome Period

- DM/PM patients used statistically significantly (p<0.001) more healthcare resources during the 12-month outcome period than matched controls (**Figure 2**)
- Medical visits
  - In the year following diagnosis, DM/PM patients had an average of 31.0 medical visits compared with 23.6 visits among matched non-DM/PM controls; approximately 57% of the additional medical visits were directly attributable to DM/PM-related care (4.2 of the 7.4 visit differential)
  - DM/PM patients had 44.0% more inpatient admissions (3.6 vs. 2.5), 33.3% more ED visits (0.8 vs. 0.6), and 26.7% more outpatient/physician office visits (21.8 vs. 17.2) compared with matched non-DM/PM controls (**Figure 3**)
  - DM/PM patients also had significantly more rheumatologist (1.8 vs. 0.6), neurologist (0.8 vs. 0.4), and physical therapy (3.7 vs. 2.6) visits compared with matched controls (data not shown)
- Prescription drug use
  - On average, DM/PM patients filled on average 4.7 more prescriptions than matched non-DM/PM controls during the outcome period (32.2 vs. 27.5 fills, p<0.001)

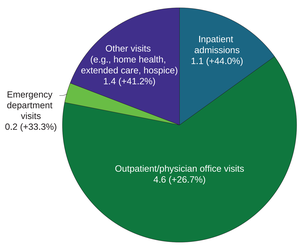
DM/PM patients incurred significantly more healthcare resource utilization relative to matched controls

Figure 2. Healthcare resource utilization during the outcome period



* Difference statistically significant at the 0.001 level.

Figure 3. Components of per-patient annual healthcare resource utilization differential*

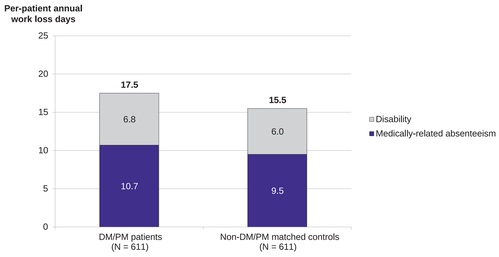


* All differences statistically significant at the 0.001 level.

Medically-Related Work Loss During the Outcome Period

DM/PM patients had 2.0 more days of work loss than matched controls, which was predominantly driven by medically-related absenteeism

Figure 4. Disability and medically-related absenteeism during the outcome period*



* Difference in overall number of work loss days and medically-related absenteeism statistically significant at the 0.001 level. Difference in number of disability days not significant (p=0.977).

LIMITATIONS

- The results of this analysis likely understate the actual burden of DM/PM in the US
  - This study was limited to resource use differentials in the 12 months following DM/PM diagnosis only
  - The matching process disproportionately removed DM/PM patients with relatively high HCRU and control patients with relatively low HCRU
  - The analysis excludes additional indirect burden (e.g., quality of life, "presenteeism")
- As with any claims data analysis, this analysis relied on ICD-9 and CPT codes to identify diagnoses and procedures as opposed to actual observance of diagnoses and resource use
- Work loss information could only be estimated for a subset of primary beneficiaries; the calculation by definition is limited to the employed population
- The study was based on a population of commercially-insured beneficiaries, and the generalizability to other patient populations (e.g., Medicaid, Medicare) is unknown

CONCLUSION

- This study is the first to use rigorous methodologies to estimate incremental burden of DM/PM using recent, nationally representative administrative claims data, controlling for a broad set of underlying differences between DM/PM and control populations
- DM/PM imposes a significant increase in healthcare resource use burden and is associated with statistically significantly greater work loss in the first year of diagnosis
- These findings of resource use in DM/PM are consistent with, though slightly higher than, prior research of resource use in similar chronic musculoskeletal diseases, such as rheumatoid arthritis, psoriatic arthritis, and osteoporosis[11–13]

REFERENCES

1. Dalakas, M.C. and R. Hohlfeld. Polymyositis and dermatomyositis. *Lancet*, 2003. 362(9388): p. 971–82.
2. Jacobson, D.L., et al., Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol*, 1997. 84(3): p. 223–43.
3. Bernatsky, S., et al., Estimating the prevalence of polymyositis and dermatomyositis from administrative data: age, sex and regional differences. *Ann Rheum Dis*, 2009. 68(7): p. 1192–6.
4. Regardt, M., et al., Patients with polymyositis or dermatomyositis have reduced grip force and health-related quality of life in comparison with reference values: an observational study. *Rheumatology* (Oxford), 2011. 50(3): p. 578–85.
5. Marie, I., et al., Interstitial lung disease in polymyositis and dermatomyositis. *Arthritis Rheum*, 2002. 47(6): p. 614–22.
6. Barnes, B.E., Dermatomyositis and Malignancy: A Review of the Literature. *Ann Intern Med*, 1976. 84(1): p. 68–76.
7. Hill, C.L., et al., Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet*, 2001. 357(9250): p. 96–100.
8. Tisseverasinghe, A., S. Bernatsky, and C.A. Pineau, Arterial events in persons with dermatomyositis and polymyositis. *J Rheumatol*, 2009. 36(9): p. 1943–6.
9. Marie, I., Morbidity and mortality in adult polymyositis and dermatomyositis. *Curr Rheumatol Rep*, 2012. 14(3): p. 275–85.
10. Austin, P.C., An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*, 2011. 46(3): p. 399–424.
11. United States Bone and Join Initiative, *The Burden of Musculoskeletal Diseases in the United States, Third edition*, 2014. Rosemont, IL.
12. Feldman, S.R., et al., Economic and comorbidity burden among moderate-to-severe psoriasis patients with comorbid psoriatic arthritis. *Arthritis Care Res*, 2015. 67(5): p. 709–17.
13. Merkesdal, S., et al., Indirect cost assessment in patients with rheumatoid arthritis (RA): comparison of data from the health economic patient questionnaire HEQ-RA and insurance claims data. *Arthritis Rheum*, 2005. 53(2): p. 234–40.

Presented at the AMCP Nexus, Orlando, Florida, 26–29 October 2015. This study was supported by Mallinckrodt Pharmaceuticals.