Repository Corticotropin Injection (RCI) Attenuates Disease Activity In Patients With Persistently Active Systemic Lupus Erythematosus (SLE) Requiring Corticosteroids: Results From A 44-Week Open-Label Extension Study

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BACKGROUND

- 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 leukocyte 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 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 suggest that RCI, but not Placebo, attenuated IL4/CD40L-induced proliferation and immunoglobulin production in B lymphocytes isolated from healthy human volunteers [6]
- We recently reported results from a pilot 8-week randomized double-blind (DB) placebo (PBO)-controlled study of RCI (NCT01753401) in subjects with persistently active SLE including rash and/or arthritis, despite moderate dose corticosteroids [7]. Although the primary endpoint of this study (resolution of disease activity for SLEDAI rash or arthritis with no worsening of other organ systems by BILAG) was not met, RCI therapy led to improvement in several measures of disease activity, including total hybrid SLEDAI (hSLEDAI), total BILAG, CLASI Activity scores, and Tender and Swollen Joint Count, as compared with PBO. This study included a 44-week open-label extension (OLE), with topline results from the OLE reported here.

References

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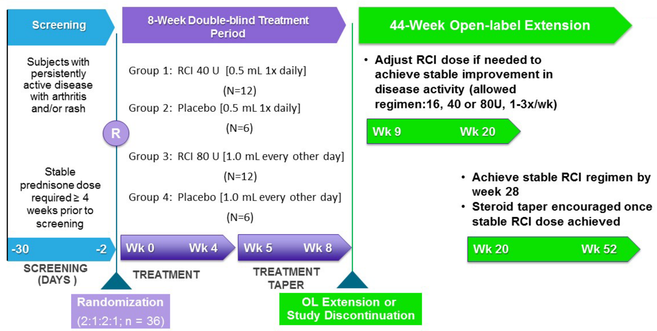
STUDY POPULATION

- Any subject who completed the 8-week double-blind, PBO-controlled randomized phase of the study, whether randomized to RCI or PBO

STUDY DESIGN

- Initial RCI dose in the OLE was based on study drug regimen at the completion of the DB phase of the study (16, 40 or 80 U 2x/wk)
- RCI dose adjustment was allowed with the goal of a stable RCI regimen by week 20, but no later than week 28
- Steroid dose adjustment was not allowed until stable RCI regimen achieved (week 20-28)
- Steroid taper was encouraged but not required after stable RCI regimen achieved
- Taper of other immunosuppressants was allowed after attempts at steroid taper



Formal sample size calculations were not performed for this pilot study

KEY OUTCOME MEASURES*

- Proportion of responders, 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, immediately prior to initiating steroid taper (if steroid taper was initiated)
- Change in hSLEDAI from OLE baseline
- Change in total BILAG-2004 score from OLE baseline
- Change in PGA from OLE baseline
- Change in tender and swollen joint counts from OLE baseline for subjects with score >0 at OLE baseline
- Change in CLASI Activity score from OLE baseline for subjects with score >0 at OLE baseline
- Proportion of patients achieving a reduction in daily prednisone dose to < 7.5 mg/day at Week 52
- Proportion of patients achieving a 50% reduction in daily prednisone dose at Week 52

Post hoc analyses:

- Proportion of patients meeting the SLE Responder Index (SRI) definition at Weeks 20 and 52
- Rate of severe flare based on SFI score at Weeks 20 and 52

Safety endpoints:

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

Analysis:

- Quantitative endpoints were summarized at each time point using mean, SD, median, minimum value, and maximum value.
- Categorical endpoints were summarized using frequency counts and percentages

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

RESULTS

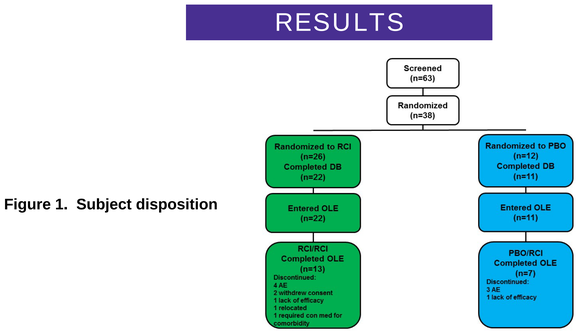


Figure 1. Subject disposition

Table 1. Demographics and disease characteristics of the mITT population at OLE baseline

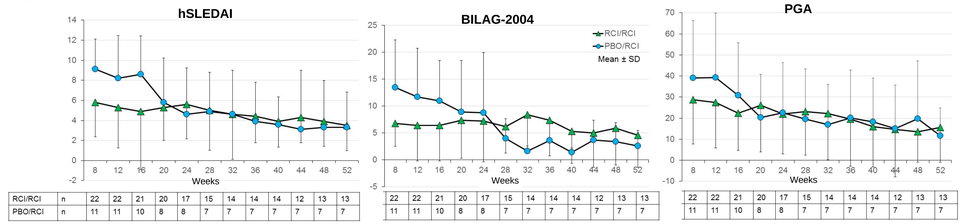
Parameter		RCI/RCI (n=22)	PBO/RCI (n=11)
Age (yr)	Mean (SD)	42.8 (9.72)	31.9 (9.05)
Female	n (%)	21 (95.5)	10 (90.0)
Caucasian/African American	n (%)	16 (72.7)/5(22.7)	5 (45.5)/ 6 (54.5)
Hybrid SLEDAI*	Mean (SD)	5.8 (3.02)	9.1 (3.42)
BILAG-2004 (total score)	Mean (SD)	6.8 (4.31)	13.5 (8.82)
CLASI Activity score	Mean (SD)	3.7 (4.24)	5.7 (6.87)
Tender & Swollen Joint Count	Mean (SD)	1.0 (2.10)	1.8 (2.99)
Physician Global Assessment (PGA) (mm)	Mean (SD)	28.7(21.05)	39.1 (27.24)
Prednisone (mg/day)	Mean (SD)	9.0 (1.67)	16.4 (8.09)
Antimalarials	n (%)	16 (72.7)	7 (63.6)
Immunosuppressants	n (%)	4 (18.2)	6 (54.5)

CONCLUSIONS

These data demonstrate that subjects who continued on RCI throughout the 44 week OLE had a durable response to therapy, while subjects who crossed over from PBO to RCI experienced improvements in several measures of disease activity during the OLE. These improvements were generally comparable to the improvements seen with RCI treatment from the blinded phase of the trial by 12-16 weeks after RCI was initiated. Limitations of this study include the small sample size, lack of blinding, and lack of a comparator group. However, taken together, the data from this pilot study support the efficacy of RCI as a potential treatment option in SLE patients who have persistent disease activity despite corticosteroid therapy, and provide the foundation for the design and execution of a well-powered trial of RCI in active SLE.

RESULTS

Figure 2. Disease activity measures over time



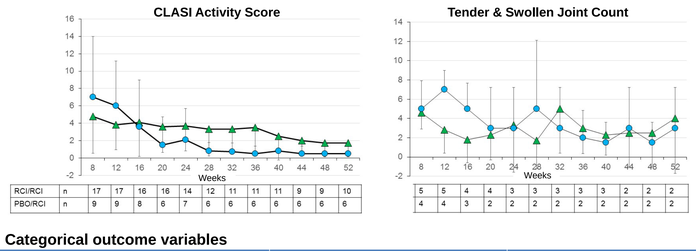


Table 2. Categorical outcome variables

Parameter	RCI/RCI (n=22)	PBO/RCI (n=11)
proportion of observed cases (%)		
SLEDAI rash or arthritis domain 0 & no new BILAG prior to steroid taper*	5/10 (50)	2/7 (28.6)
SRI Response (week 52)	10/13 (76.9)	6/7 (85.7)
Prednisone to <7.5 mg/day (week 52)	9/13 (69.2)	3/7 (42.9)
Prednisone decreased > 50% (week 52)	7/13 (53.8)	4/7 (57.1)
proportion based on mITT (%)		
SRI Response (week 52)**	10/22 (45.5)	6/11 (54.5)
Prednisone to <7.5 mg/day (week 52)**	9/22 (40.9)	3/11 (27.3)
Prednisone decreased > 50% (week 52)**	7/22 (31.8)	4/11 (36.4)
Severe flares (SFI) (week 52)	2/22 (9.1)	3/11 (27.3)

* Excludes subjects who did not initiate steroid taper during the OLE, **Missing data and dropouts imputed as nonresponse

Table 3. Overall Summary of Treatment-Emergent Adverse Events during OLE

Parameter		RCI/RCI (n=22)	PBO/RCI (n=11)
Any TEAE	n (%)	19 (86.4)	8 (72.7)
Any severe TEAE*	n (%)	1 (4.5)	2 (18.2)
Any treatment-related AE**	n (%)	7 (31.8)	2 (18.2)
Any TEAE leading to study discontinuation	n (%)	3 (13.6)	2 (18.2)
Any serious TEAE	n (%)	2 (9.1)	4 (36.4)
Any TEAE resulting in death	n (%)	0	0

AE = adverse event; AEs classified into system organ class and preferred terms using MEDRA v15.1; * AEs were considered severe if the severity of an event was missing; ** Adverse Events were considered treatment-related if the relationship to study medication was possibly related, probably related, definitely related, or missing

No new safety signals were reported.

- Two RCI/RCI subjects experienced SAEs – pelvic abscess and lower abdominal pain/pelvic infection.
- Four PBO/RCI subjects experienced SAEs – viral infection, non-cardiac chest pain, pyelonephritis and SLE flare with hospitalization.

Author Disclosure Information: R.A. Furie is an Investigator and consultant for Mallinckrodt Pharmaceuticals, Inc, M. Mitrane is a consultant to Mallinckrodt Pharmaceuticals, Inc., E. Zhao is a full time employee of Mallinckrodt Pharmaceuticals, and P.M. Becker is a full time employee and owns stock or stock options in Mallinckrodt Pharmaceuticals.
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