Dear Healthcare Professional,

Thank you for your unsolicited request for information. Accompanying this letter is the following information you requested on Purified Cortrophin® Gel. If we can be of any further assistance, please contact our Medical Information department at (844) CORT-GEL (844-267-8435) between the hours of 9:00 AM to 7:00 PM ET (6:00 AM to 4:00 PM PT), Monday through Friday or via email at cortrophinmedinfo@anipharmaceuticals.com.

Purified Cortrophin Gel is indicated in the following disorders:

1. 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.
- Acute gouty arthritis.

2. Collagen diseases:
During an exacerbation or as maintenance therapy in selected cases of:
- Systemic lupus erythematosus.
- Systemic dermatomyositis (polymyositis).

3. Dermatologic diseases:
Severe erythema multiforme (Stevens-Johnson syndrome).
Severe psoriasis.

4. Allergic states:
Atopic dermatitis
Serum sickness.

5. Ophthalmic diseases:
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
- Allergic conjunctivitis.
- Keratitis.
- Iritis and iridocyclitis.
- Diffuse posterior uveitis and choroiditis.
- Optic neuritis.
- Chorioretinitis.
- Anterior segment inflammation.

6. Respiratory diseases:
Symptomatic sarcoidosis.

7. Edematous states:
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.

8. Nervous system:
Acute exacerbations of multiple sclerosis.

Purified Cortrophin Gel is contraindicated for intravenous administration.

Purified Cortrophin Gel is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, hypertension, or sensitivity to proteins derived from porcine sources.

Purified Cortrophin Gel is contraindicated in patients with primary adrenocortical insufficiency or adrenocortical hyperfunction.

Please see the enclosed Purified Cortrophin Gel Prescribing Information (PI) for detailed information including Warnings and Precautions and Adverse Reactions as well as the appropriate use of Purified Cortrophin Gel.

Thank you for your inquiry.

Sincerely,

Steve Wu, PharmD
ANI Pharmaceuticals Medical Information

Use of Purified Cortrophin® Gel (Repository Corticotropin Injection USP) 80 U/mL in Adults With Systemic Lupus Erythematosus

Literature Search

- Summarized in this document are published clinical studies using natural-product corticotropins other than Cortrophin Gel.
  - To ensure comprehensive coverage of the topic, a search of clinical publications was conducted on PubMed. The search included all clinical publications from 1952 to January 2023 on the use of ACTH for treating patients with systemic lupus erythematosus (SLE). These criteria were designed to identify all relevant studies on the topic and to provide a comprehensive overview of the use of ACTH for the treatment of SLE. A total of nine studies were identified, which represented 167 patients who received ACTH for SLE treatment. These studies included randomized controlled trials, open-label studies, and case reports.

Note that this document is for information purposes only. This document may contain information not included in the prescribing information for Cortrophin Gel. The usage of corticotropin being discussed may not have been approved by the FDA as safe and effective. ANI Pharmaceuticals does not recommend the use of its products in any manner inconsistent with the FDA-approved labeling.

To report an adverse event for any ANI Pharmaceuticals product, please call 1-800-308-6755 or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Email: drugsafety@anipharmaceuticals.com.

Background

Purified Cortrophin Gel (Repository Corticotropin Injection USP) is approved by the FDA for the treatment of collagen diseases, such as SLE.[1]

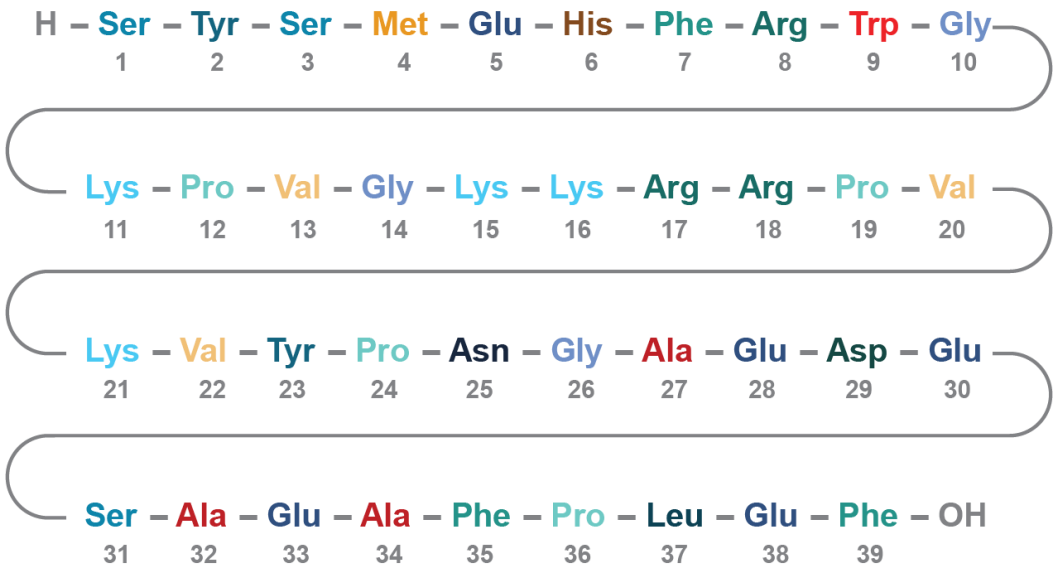
- The active agent in Cortrophin Gel is porcine-derived adrenocorticotropic hormone (ACTH peptide, amino acids 1-39), which is biologically similar to endogenous, human ACTH,[2] and of the same class as other, FDA-approved, natural-product and synthetic corticotropins.

Composition of Cortrophin Gel[1]

Cortrophin Gel is a porcine-derived purified corticotropin (ACTH) in a sterile solution of gelatin. It is made up of a complex mixture of ACTH, ACTH-related peptides and other porcine pituitary-derived peptides.

The drug product is a sterile preparation containing 80 USP units per mL and it contains 0.5% phenol (as preservative), 15.0% gelatin (for prolonged activity), water for injection, and the pH is adjusted with hydrochloric acid and sodium hydroxide.

Cortrophin Gel contains the porcine-derived ACTH (1-39) with the following amino acid sequence:



To obtain FDA approval, following guidance of the FDA, ANI conducted a study on the pharmacodynamic effect of Cortrophin Gel, including C_{max}, $AUEC_t$, and T_{max}, and compared it with the response of the same or similar depot structures from published literature for bioequivalence.[3]

Clinical Data of Cortrophin Gel in SLE

Below are publicly available clinical studies using Acthar® Gel, which shares the same porcine-derived active agent as Cortrophin Gel. The below summary provides an overview of the published clinical evidence of in-class ACTH-based therapies, with references to source material.

A search of clinical publications was conducted on PubMed. The search included all clinical publications from 1952 to January 2023 on the use of ACTH for treating patients with SLE. These criteria were designed to identify all relevant studies on the topic and to provide a comprehensive overview of the use of ACTH for the treatment of SLE. A total of nine studies were identified, which represented 167 patients who received ACTH for SLE treatment. These studies included randomized controlled trials, open-label studies, and case reports (**Tables 1 and 2**).

Table 1. Summary of Clinical Data in Support of Cortrophin Gel Use in Patients With SLE

Study	Objective	Design	ACTH, n	Comparator, n	Patient Population	Study Tx Regimen	Efficacy	Safety
Fiechtner 2014[4]	Acthar Gel was evaluated for its effectiveness in lowering active SLE severity in individuals receiving underlying conventional maintenance treatments.	Prospective: a single-site, open-label trial	10	N/A	Patients who met the ACR criteria for SLE and who presented with chronic, moderate to severe active SLE and a disease flare during standard treatment. Duration of SLE ranged from 1 to 16 years.	80 IU SC QD for 10 days, with an optional 5-day rescue period for partial or nonresponders, as determined by the principal investigator.	Statistically significant improvements at all follow-up visits for physician global assessment, patient global assessment, SLEDAI-2K, FACIT-Fatigue, and ESR were observed (all *P*<0.05).	No treatment-related serious or unexpected adverse events were reported for the duration of the trial.
Li 2015[5]	To understand the function of Acthar Gel as a therapy for SLE	Retrospective study	9	N/A	Patients diagnosed with SLE. Duration of SLE ranged from 3 to 19 years.	80 IU SC biweekly for 3 to 6 months	7/9 patients had overall improvement. After 6 months, there was an overall reduction of 40.2% in the individual SLEDAI-2K scores of 8 patients. Four patients had an improvement or resolved arthritis; one patient had resolved inflammatory rash.	Investigators did not indicate whether a safety assessment was performed.
Furie 2016[6]	To compare the effectiveness and safety of RCI in patients with persistent active SLE who required moderate-dose corticosteroids.	Double-blinded, randomized, controlled pilot study	22	Placebo (11)	Patients diagnosed with SLE who have active disease with arthritis and rash based on the hSLEDAI. Patients were also required to have a BILAG score of A or B.	40 IU SC QD or 80 IU SC QOD for 8 weeks	By weeks 6 to 8, RCI outperformed placebo in established outcome measures such as change from baseline in overall hSLEDAI (40 IU, *P*=0.026; 80 IU, *P*=0.020) and total BILAG score (40 IU, *P*=0.005; 80 IU, *P*=0.002).	AEs: weight gain, abdominal pain, back pain, diarrhea, fatigue, fluid retention, irritability, and mood swings. TEAEs: treatment was discontinued in one patient receiving RCI 40 IU and one patient receiving RCI 80 IU. The patient in the 40 IU group experienced mild chest discomfort and moderate gastro-esophageal reflux disease. The patient in the 80 IU group was discontinued due to a false-positive hepatitis C test result. The patient

								died of severe Klebsiella sepsis with multi-organ failure, this event was deemed improbable to be associated with the study medication.
Furie 2017[7]	Over 52 weeks, post hoc analysis was performed to assess the efficacy of RCI in patients with SLE.	Post hoc analysis of results from a two-part, 52-week pilot study (8-week, randomized, double-blind, placebo-controlled treatment period followed by a 44-week OLE). This is a follow-up study to Furie 2016.	20	Placebo (11)	Patients diagnosed with SLE who have active disease with arthritis and rash based on the hSLEDAI. Patients were also required to have a BILAG score of A or B.	40 IU SC QD or 80 IU SC QOD for 8 weeks. In the OLE phase, patients received 16, 40 or 80 IU RCI twice weekly	Individuals who switched from placebo to RCI at the start of the OLE exhibited improvements in disease activity measures equivalent to patients who received RCI throughout the first 8 weeks of the trial.	In addition to the TEAEs reported by Furie 2016 in the RCI/RCI group of the double-blind phase, over the course of the OLE phase, one patient reported pelvic infection and lower abdominal pain. Another patient had pelvic abscess. Four placebo/RCI patients also reported TEAEs, including viral infection, noncardiac chest pain, pyelonephritis, and hospitalization due to a flare of SLE.
Askanase 2020[8]	To evaluate the effectiveness and safety of RCI in patients with persistently active SLE despite moderate-dose glucocorticoids	Multicenter, double-blind, randomized, placebo-controlled study	73	Placebo (71)	Patients 18 years or older with active SLE with moderate to severe rash and/or arthritis. Time since diagnosed with SLE: RCI group (7.6 $\pm$ 6.8 years) and placebo group (5.8 $\pm$ 5.0 years).	80 IU SC QOD through week 4, then twice weekly through week 24	The proportion of SRI-4 responders at week 16 was not significantly different between groups (RCI, 47.6%; placebo, 43.5%; OR [95% CI] 1.2 [0.6 to 2.2]; *P*=0.5762). However, RCI therapy reduced the SJC/TJC and CLASI-Activity scores from baseline to week 16 and the B-cell activating factor cytokine from baseline to week 8.	The most common AEs in the RCI group were upper respiratory tract infection (10.5%), insomnia (8.1%), headache (7.0%), hypertension (7.0%), and urinary tract infection (7.0%).
Askanase 2021[9]	To evaluate patient-reported outcomes and report the post hoc analyses that offer more insight into the impact of RCI on the quality of life and work						RCI was associated with greater improvements in the LupusQoL pain, planning, fatigue domain, and presenteeism (percentage impairment	Investigators did not indicate whether a safety assessment was performed.

	productivity of patients with elevated disease activity.						while working) compared to placebo.	
Ho-Mahler 2021[10]	To understand the practice patterns and outcomes of RCI in patients with SLE.	Retrospective study	30	N/A	Patients ≥18 years diagnosed with SLE.	40 IU twice/day (n=1) 80 IU once/day (n=2) 80 IU once/week (n=4) 80 IU twice/week (n=21) Average duration of RCI treatment: 6.5 ± 2.2 months.	94.7% of physicians rated the patients as improved after treatment with RCI. The average time to best impression was 4.3 ± 2.7 months.	SAEs were reported in 4 patients: altered musculoskeletal pain, dehydration, adrenal insufficiency, pneumonia, renal failure, and transient ischemic attack.
Madan 2016[11]	To investigate the effectiveness and safety of Acthar Gel therapy in individuals with NS who have often experienced numerous unsuccessful treatments.	A multicenter retrospective case series	2	N/A	Patients with SLE class V membranous lupus nephritis.	80 IU twice weekly for ≥6 months	Both patients showed ≥50% reduction in proteinuria (86.4% and 87.7% reduction) and partial remission post-Acthar Gel treatment. Serum albumin also increased post-treatment.	Investigators did not indicate whether a safety assessment was performed.
Bomback 2011[12]	To investigate the use of Acthar Gel for NS in the United States.	Retrospective case series	1	N/A	Patients with class V SLE glomerulonephritis.	40 IU SC thrice weekly for 5 months	No response was reported in the patient. However, proteinuria dropped from 1340 mg/day to 420 mg/day during treatment. The patient's proteinuria rebounded to 2290 mg/day after treatment was stopped due to weight gain.	Weight gain.

ACR, American College of Rheumatology; BILAG, British Isles Lupus Assessment Group; CLASI, cutaneous lupus erythematosus disease area and severity index; DMARDs, disease-modifying antirheumatic drugs; FACIT-Fatigue, functional assessment of chronic illness therapy-fatigue; hSLEDAI, hybrid SLE disease activity index; IU, international unit; NS, nephrotic syndrome; OLE, open label extension; QD, once daily; QOD, once every other day; RCI, repository corticotropin injection; SC, subcutaneous; SLE, systemic lupus erythematosus; SoC, standard of care; SLEDAI-2K, systemic lupus erythematosus disease activity Index-2000; ESR, erythrocyte sedimentation rate; SRI, SLE responder index; SJC/TJC, swollen joint count/tender joint count; TEAE, treatment-emergent adverse event; WPAI, work productivity and activity impairment.

Table 2. Prior and Concomitant Medications

Study	Prior therapy	Concurrent therapy to ACTH, (%)
Fiechtner 2014[4]	All patients received either a stable dose of prednisone (or equivalent) 20 mg/day from at least four weeks prior to signing the informed consent. 70% of patients were previously treated with methylprednisolone, 60% with prednisone, 40% with methotrexate, 30% with mycophenolate mofetil, 20% with thalidomide, and 40% with hydroxychloroquine.	Belimumab (90%) Meloxicam, prednisone, hydroxychloroquine (50%) Tramadol, methotrexate (40%) Folic acid (30%) Diclofenac cream (20%) Ibuprofen, sulfasalazine, celecoxib, diclofenac sodium, hydrocortisone (10%)
Li 2015[5]	All patients received stable immunosuppressants for at least four weeks before starting Acthar Gel treatment, including five receiving oral corticosteroids. At the time of Acthar Gel administration, all patients had failed to react clinically to several immunosuppressants and/or being treated with immunosuppressants.	Hydroxychloroquine (89%) Mycophenolate mofetil (33%) Prednisone (67%) Methotrexate (33%) Belimumab (56%) Azathioprine (22%)
Furie 2016[6]	All patients received stable, moderate-dose corticosteroids for at least 4 weeks before screening (prednisone 7.5-30 mg/day, or equivalent). The average daily prednisone dosage was 10.8 g/day and 9.2 g/day in the RCI 40 IU and 80 IU groups, respectively, and 16.4 mg/day in the combined placebo group.	Corticosteroids, nonsteroidal anti-inflammatory medications, antimalarials, methotrexate, azathioprine, and mycophenolate mofetil were allowed if the eligibility conditions were satisfied, and the dosages remained constant during the 8-week trial period. The following therapies were used: • Combined RCI group: antimalarials (72%), immunosuppressants (24%), mycophenolate mofetil (12%), methotrexate (12%), and azathioprine (12%) • Combined placebo group: antimalarial (72.7%), immunosuppressants (54.5%), mycophenolate mofetil (36.4%), and methotrexate (27.3%)
Furie 2017[7]		During the 52-week study period, 33.3% of patients used immunosuppressants (azathioprine, methotrexate, or mycophenolate mofetil) and 72.2% of the patients used antimalarials. The average prednisone daily dosage was 10.0 mg/day and 16.4 mg/day in the RCI/RCI and placebo/RCI groups, respectively.
Askanase 2020[8]	Patients were enrolled if they received glucocorticoids for at least 8 weeks before screening and had been receiving stable glucocorticoid dosages of 7.5 to 30 mg of daily prednisone equivalents for at least 4 weeks prior to screening. At baseline, patients were treated with the following therapy: Prednisone ≤20 mg/day: RCI group, n=82 (97.6%); placebo, n=79 (92.9%) Prednisone >20 mg/day: RCI group, n=2 (2.4%); placebo, n=6 (7.1%) Antimalarials: RCI group, n=65 (77.4%); placebo, n=69 (81.2%) Immunosuppressants: RCI group, n=62 (73.8%); placebo, n=47 (55.3%)	Topical and/or inhaled glucocorticoids were allowed during the study period.

Askanase 2021[9]	The average baseline prednisone (range: 7.5 to 30 mg) or equivalent glucocorticoid dosage was 11.1 mg—95.3% of patients were receiving ≤20 mg/day). Some of the prior medications used by the patients include azathioprine: RCI, n=27 (32.1%); placebo, n=20 (23.5%) Methotrexate: n=27 RCI (32.1%); placebo, n=22 (25.9%) Mycophenolate mofetil: n=8 RCI (9.5); placebo, n=9 (10.6%) Mycophenolic acid: n=14 RCI (16.7%); placebo, n=10 (11.8%)	Antimalarials, NSAIDs, and immunosuppressants were allowed throughout the study.
Ho-Mahler 2021[10]	Corticosteroids n=24 (80%) Immunosuppressive drug, n=17 (57%) Monoclonal antibodies, n=14 (47%) Nonbiologic DMARDs, n=22 (73%)	None reported.
Madan 2016[11]	Prednisone, n=1 (50%) Cyclophosphamide, n=1 (50%) Mycophenolate mofetil, n=1 (50%)	Angiotensin-converting-enzyme inhibitor, n=2 (100%) Prednisone, n=1 (50%)
Bomback 2011[12]	One patient enrolled in the study previously received steroids, mycophenolate mofetil, and calcineurin inhibitor	None reported.

DMARDs, disease-modifying antirheumatic drugs; NSAIDs**,** nonsteroidal anti-inflammatory drugs**;** RCI, repository corticotropin injection.

Additional Study Details of Cortrophin Gel in Patients With SLE

Fiechtner 20144

Eligible patient population

At least 4 of the 11 ACR classification criteria for SLE must have been met, including a history of antinuclear antibody (ANA) positivity. Ten patients met the ACR criteria for SLE and presented with chronic disease requiring ongoing treatment or observation for ≥8 weeks.

Patient demographics

Prior to RCI treatment, all patients received ≤20 mg/day of either a stable dose of prednisone or equivalent for a minimum of four weeks. Seventy percent of patients were previously treated with methylprednisolone, 60% with prednisone, 40% with methotrexate, 30% with mycophenolate mofetil, 20% with thalidomide, and 40% with hydroxychloroquine. Concurrent therapies were belimumab (90%), meloxicam, prednisone, and hydroxychloroquine (50%), tramadol and methotrexate (40%), folic acid (30%), diclofenac cream (20%), and ibuprofen, sulfasalazine, celecoxib, diclofenac sodium, and hydrocortisone (10%).

Dosing

The patients received 80 IU SC once daily for 10 days, with an optional 5-day rescue period for partial or nonresponders, as determined by the principal investigator.

Response to ACTH

Following treatment with Acthar Gel, there were statistically significant improvements at all follow-up visits for physician global assessment, patient global assessment, SLEDAI-2K, FACIT-Fatigue, and ESR (all $P<0.05$).

Safety

Acthar Gel was well tolerated by the patients. No treatment-related serious or unexpected adverse events were reported for the duration of the trial. One patient reported bilateral edema in the legs and ankles, and another reported a sinus infection.

Treatment Duration and Patient Follow-Up

All the patients were assessed weekly from baseline to week 4.

Li 2015[5]

Eligible patient population

This retrospective study enrolled patients ≥18 years old diagnosed with SLE. Patients had to meet at least 4 of the eleven ACR criteria or the Systemic Lupus International Collaborating Clinics (SLICC) criteria. According to the SLICC criteria, a patient was classified with SLE if they satisfied 4 of the clinical

and immunologic criteria, which had to include at least one clinical criterion and one immunologic criterion. Alternatively, if a patient had biopsy-proven nephritis that was compatible with SLE and had ANA or anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies, they were also classified as having SLE.

Patient demographics

A total of 9 patients were enrolled in the study. Prior to Acthar Gel treatment, patients were treated with a stable dosage of immunosuppressants for at least 4 weeks. At the time of Acthar Gel administration, all patients had failed to react clinically to several immunosuppressants and/or were receiving immunosuppressants. The patients received several concurrent therapies, including hydroxychloroquine (89%), mycophenolate mofetil (33%), prednisone (67%), methotrexate (33%), belimumab (56%), and azathioprine (22%).

Dosing

The patients received 80 IU SC biweekly.

Response to ACTH

Out of the 9 patients who received treatment, 7 of them were able to taper steroids. After 6 months, there was an overall reduction of 40.2% in the individual SLEDAI-2K scores of 8 patients. Additionally, 4 out of 5 patients with arthritis showed improvement or resolution, and 1 out of 2 patients with an inflammatory rash experienced resolution.

Safety

Investigators did not indicate whether a safety assessment was performed.

Treatment Duration and Patient Follow-Up

After starting Acthar Gel treatment, patients were monitored by their doctors for at least 3 to 6 months.

Furie 2016[6]

Eligible patient population

In this double-blind, randomized, controlled study, eligible patients (age ≥18 years) were diagnosed with SLE who have active disease with arthritis and rash based on the hSLEDAI. Patients were also required to have a BILAG score of A or B in the musculoskeletal or mucocutaneous domains and be seropositive for ANAs, anti-dsDNA, anti-Smith, or anti-cardiolipin antibodies.

Patient demographics

This study enrolled 38 patients with persistently active SLE. All patients were receiving stable, moderate-dose corticosteroids for at least 4 weeks before screening (prednisone 7.5 to 30 mg/day, or equivalent). The average daily prednisone dosage was 10.8 g/day and 9.2 g/day in the RCI 40 IU and 80 IU groups, respectively, and 16.4 mg/day in the combined placebo group. Concurrently with RCI therapy, 72% of the patients were treated with an antimalarial, and 12% received either mycophenolate mofetil, methotrexate, or azathioprine. In the placebo group, 72.7% of patients received an antimalarial

concurrent with RCI, 54.5% received immunosuppressants, 36.4% received mycophenolate mofetil, and 27.3% were receiving methotrexate.

Dosing

Participants received either RCI 40 IU SC QD, RCI 80 IU SC QOD, or volume-matched placebo gel. Between weeks 1 to 4, if predetermined safety requirements were identified, the dosage volume could be reduced, corresponding to RCI doses of 16 IU QD and 40 IU QD in the 40 IU QD and 80 IU QD groups, respectively. The doses were tapered between weeks 5 to 8, lowering the frequency of administration such that by the end of the double-blind period, all patients were receiving 2 doses per week.

Response to ACTH

At week 4, there was no significant difference in response between the combined placebo and RCI-treated groups, as defined by the primary outcome which was a novel composite responder index defined as the percentage of patients responding to treatment by week 4. However, by weeks 6 to 8, RCI outperformed placebo in established outcome measures such as change from baseline in overall hSLEDAI (40 IU, *P*=0.026; 80 IU, *P*=0.020; combined RCI group, *P*=0.008) and total BILAG score (40 IU, *P*=0.005; 80 IU, *P*=0.002; combined RCI group, *P*=0.001). Furthermore, the proportion of patients who improved their BILAG mucocutaneous or musculoskeletal domain scores in the RCI 80 IU group was considerably greater than in the combined placebo groups (83.3% vs 36.4%, *P*=0.036).

Safety

Weight gain (19.4% of patients) was the most common AE reported. 23.1% of patients in the RCI group reported an infection compared with 9.1% in the placebo group. Other AEs reported were abdominal pain, back pain, diarrhea, fatigue, fluid retention, irritability, and mood swings. Treatment was discontinued in 1 patient receiving RCI 40 IU and 1 patient receiving RCI 80 IU. The patient in the 40 IU group experienced mild chest discomfort and moderate gastro-esophageal reflux disease. The patient in the 80 IU group was discontinued due to a false-positive hepatitis C test result. The patient died of severe Klebsiella sepsis with multi-organ failure. This event was deemed improbable to be associated with the study medication. One patient in the RCI 80 IU group had 2 SAEs: a hemorrhagic ovarian cyst and a viral infection, which were considered unrelated to the study therapy.

Treatment Duration and Patient Follow-Up

The study lasted for 8 weeks.

Furie 2017[7]

Eligible patient population

Furie 2017 was a continuation of Furie 2016. Both studies looked at the same set of patients and had the same eligible patient populations.

Patient demographics

Out of the 38 patients enrolled in the double-blinded phase, 33 patients completed week 8 and entered the OLE phase (RCI/RCI: n=22, placebo/RCI: n=11), and 20 patients completed treatment through week 52 (RCI/RCI: n=13, placebo/RCI: n=7). During the 52-week treatment period, 33.3% of patients were treated with immunosuppressants (azathioprine, methotrexate, or mycophenolate mofetil) and 72.2% of the patients were treated with antimalarials. The average prednisone dose was 10.0 mg/day and 16.4 mg/day in the RCI/RCI and placebo/RCI groups, respectively.

Dosing

Patients were randomized to receive either RCI 40 IU SC QD, 80 IU QOD, or volume-matched placebo by subcutaneous injection during the double-blind phase. Based on the trial dosing regimen at the end of the double-blind phase at week 8, the first RCI dose in the OLE was determined. Patients who received RCI 16 IU, 40 IU, or 80 IU or a placebo at week 8 started the OLE phase with RCI 16 IU, 40 IU, or 80 IU, respectively, twice weekly.

Response to ACTH

Patients who switched from placebo to RCI at the start of the OLE exhibited improvements in signs and symptoms equivalent to patients who received RCI throughout the OLE phase. Over 52 weeks, RCI patients demonstrated consistent improvement in results across multiple outcome measures, including the SLEDAI and BILAG indices. At weeks 8 and 52, the proportions of patients defined as responders in the RCI/RCI group using the revised novel composite BILAG index were 60% (15/25) and 48% (12/25), respectively. At the end of week 52, 36.0% (9/25) of patients in the RCI/RCI group had reduced their daily prednisone dosage to 7.5 mg.

Safety

In addition to the TEAEs reported by Furie 2016 in the RCI/RCI group of the double-blind phase, over the course of the OLE phase, 1 patient reported pelvic infection and lower abdominal pain. Another patient had pelvic abscess. Four placebo/RCI patients also reported TEAEs, including viral infection, noncardiac chest pain, pyelonephritis, and a hospitalization due to a flare of SLE.

Treatment Duration and Patient Follow-Up

The study lasted for 52 weeks—the double-blinded phase lasted for 8 weeks, while the OLE phase lasted for 44 weeks.

Askanase 2020[8]

Eligible patient population

This multicenter, double-blind, randomized, placebo-controlled study enrolled patients 18 years or older with active SLE with moderate to severe rash and/or arthritis. Patients were allowed to enroll if they had been receiving glucocorticoids for at least 8 weeks prior to screening and had been receiving stable glucocorticoid doses of 7.5 to 30 mg of daily prednisone equivalents for at least 4 weeks. Patients receiving a stable dose of antimalarials or NSAIDs for at least 4 weeks and/or immunosuppressants for at least 8 weeks before screening were also allowed to enroll in the study.

Patient demographics

At baseline, 97.6% of patients in the RCI group and 92.9% in the placebo group were receiving ≤20 mg/day of prednisone. 2.4% of the patients in the RCI group and 7.1% of the placebo group received >20 mg/day of prednisone. 77.4% and 81.2% of the patients in the RCI and placebo groups were receiving an antimalarial, respectively. Additionally, 73.8% and 55.3% of the patients in the RCI and placebo groups were taking immunosuppressants, respectively. Topical and/or inhaled glucocorticoids were allowed during the study period.

Dosing

Patients received 80 IU SC QOD until week 4, followed by 80 IU twice weekly until week 24.

Response to ACTH

The proportion of SRI-4 responders at week 16 was not significantly different between groups (RCI, 47.6%; placebo, 43.5%; OR [95% CI] 1.2 [0.6 to 2.2]; *P*=0.5762). However, RCI therapy reduced the SJC/TJC and CLASI-Activity scores from baseline to week 16 and the B-cell activating factor cytokine from baseline to week 8.

Safety

The most common AEs reported in the RCI group were upper respiratory tract infection (10.5%), insomnia (8.1%), headache (7.0%), hypertension (7.0%), and urinary tract infection (7.0%). Serious adverse events in the RCI group included Herpes zoster (n=1) and NS (n=1). Treatment with RCI was discontinued due to drug hypersensitivity (n=1) and NS (n=1). One patient in the placebo-treated group died due to an AE related to drug abuse.

Treatment Duration and Patient Follow-Up

All patients were treated for 24 weeks.

Askanase 2021[9]

Askanase 2021 was a continuation of Askanase 2020. Both studies looked at the same set of patients and had the same eligible patient populations, patient demographics, dosing, treatment duration, and patient follow-up.

Response to ACTH

RCI was associated with greater improvements in the LupusQoL pain, planning and fatigue domain, and presenteeism (ie, percentage of patients with impairments while working) compared to placebo. RCI had a greater impact on QoL in patients with higher disease activity at baseline, as measured by SLEDAI-2K, CLASI-Activity, and BILAG-2004 scores.

Ho-Mahler 2021[10]

Eligible patient population

This retrospective study included patients who were ≥18 years old with a physician diagnosis of SLE. These patients were required to have been administered RCI during an exacerbation or as maintenance therapy.

Patient demographics

This study included 30 patients with SLE. Prior to RCI, 80% of the patients were receiving corticosteroids, 57% were receiving immunosuppressive drugs, 47% were receiving monoclonal antibodies, and 73% were receiving nonbiologic DMARDs.

Dosing

One patient received 40 IU twice daily, 2 patients received 80 IU QD, 4 patients received 80 IU once per week, and 21 patients received 80 IU twice per week.

Response to ACTH

94.7% of physicians rated the patients as improved after treatment with RCI. The average time to best impression was 4.3 months.

Safety

Five patients reported AEs, including diarrhea, gastrointestinal upset, edema, neuralgia, pneumonia, and weight gain. SAEs were reported in 4 patients, including altered musculoskeletal pain, dehydration, adrenal insufficiency, pneumonia, renal failure, and transient ischemic attack.

Treatment Duration and Patient Follow-Up

The average duration of RCI treatment was 6.5 ± 3.3 months.

Madan 2016[11]

Eligible patient population

This multicenter retrospective case series involved 2 patients diagnosed with SLE.

Patient demographics

Prior to Acthar Gel treatment, 1 patient received prednisone and cyclophosphamide. The other patient received mycophenolate mofetil. Concurrently with Acthar Gel, 1 of the patients received an

angiotensin-converting-enzyme inhibitor and prednisone and the other received only an angiotensin-converting-enzyme inhibitor.

Dosing
The patients received 80 IU twice weekly.

Response to ACTH
Both patients showed ≥50% reduction in proteinuria (86.4% and 87.7% reduction) and partial remission post-Acthar Gel treatment, with the average proteinuria reduced by 12173.5 ± 7442.3 mg/day. Although the patients did not have renal insufficiency, they had hypoalbuminemia at baseline (1.7 and 1.8 g/dL), which improved after treatment (3.3 and 2.4 g/dL). Serum albumin also increased post-treatment.

Safety
Investigators did not indicate whether a safety assessment was performed.

Treatment Duration and Patient Follow-Up
The 2 patients were treated for ≥6 months.

Bomback 2011[12]

Eligible patient population
This retrospective case series included a single patient with class V SLE glomerulonephritis.

Patient demographics
The patient had previously received steroids, mycophenolate mofetil, and a calcineurin inhibitor.

Dosing
The patient received 40 IU 3 times per week.

Response to ACTH
No response was reported in the patient. However, during treatment, proteinuria dropped from 1340 mg/day to 420 mg/day. The patient's proteinuria rebounded to 2290 mg/day after treatment was stopped due to weight gain.

Safety
The treatment was stopped due to weight gain.

Treatment Duration and Patient Follow-Up
The patient was treated for 5 months.

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