Introduction

Although corticosteroids are the standard first-line therapy for pulmonary sarcoidosis, long-term and high-dose use of these drugs are associated with increased risk of adverse events and high healthcare utilization costs. Treatment guidelines for pulmonary sarcoidosis indicate that off-label immunomodulators and biologics may be warranted for severe disease. Repository corticotropin injection (RCI, Acthar® Gel), a complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides, is one of only two therapies approved by the US Food and Drug Administration for symptomatic pulmonary sarcoidosis and is recommended by current European Respiratory Society treatment guidelines for use on a case-by-case basis. With its unique anti-inflammatory and immunomodulatory mechanism of action through activation of melanocortin receptors in various cell types, RCI has demonstrated steroid-sparing properties. RCI has a long history of use in autoimmune and inflammatory disorders, with proven safety and efficacy for pulmonary sarcoidosis. In this narrative review, we present the clinical evidence for the safety and efficacy of RCI in the treatment of pulmonary sarcoidosis, identify where RCI falls within the current treatment guidelines, and describe the unique mechanism of action of RCI for promoting anti-inflammatory and immunomodulatory effects.

Keywords: Acthar Gel; Pulmonary; RCI; Repository corticotropin injection; Sarcoidosis
Key Summary Points

This narrative review summarizes recent clinical practice guidelines on the treatment of pulmonary sarcoidosis, as well as mechanistic and clinical data supporting repository corticotropin injection (RCI) as a safe and effective treatment option.

Multiple therapeutic options exist, including methotrexate, azathioprine, leflunomide, mycophenolate, and infliximab; however, only corticosteroids and RCI are approved by the US Food and Drug Administration for the treatment of sarcoidosis.

RCI uniquely binds and activates melanocortin receptors on adrenocortical cells and various types of immune cells to promote anti-inflammatory and immunomodulatory effects.

RCI is steroid-sparing for patients with sarcoidosis, most of whom reduced their steroid dosages by >50% in three clinical trials, and has been shown to be safe and effective for treatment of sarcoidosis that was nonresponsive to corticosteroids.

A recent expert panel using a modified Delphi process found that RCI is most commonly used in clinical practice as a second-line treatment for sarcoidosis after steroids, while European Respiratory Society (ERS) guidelines recommend that RCI be used on a case-by-case basis.

INTRODUCTION

Sarcoidosis is an inflammatory disorder characterized by granuloma formation that can affect any organ in the body, but it is most commonly observed in the lungs [1, 2]. The prevalence of sarcoidosis in the US is estimated to be 60 per 100,000 adults and varies by geographical location, age, sex, and ethnicity, with African American women having the highest prevalence of 142 per 100,000 [3, 4]. Eighty to ninety percent of patients with sarcoidosis have lung or mediastinal lymph node involvement, which are characteristic of pulmonary sarcoidosis [4]. The prevalence of pulmonary sarcoidosis in Denmark and Sweden has been estimated at 48–68 per 100,000 [5].

The manifestations of sarcoidosis are highly variable, with the course of the disease often being unpredictable [6]. Although some patients with sarcoidosis have spontaneous remission without treatment, a large proportion of patients have substantial morbidity, with 5–10% of these cases resulting in death [7]. The mortality with sarcoidosis is generally attributable to major organ damage [7]. Pulmonary fibrosis contributes to more than half of sarcoidosis fatalities, and cardiac sarcoidosis is also a major contributor to sarcoidosis deaths [8]. Neurologic sarcoidosis is associated with extensive morbidity but low mortality [7].

Guidelines are available to aid practitioners in the diagnosis, detection, and treatment of sarcoidosis [9–13], including an official American Thoracic Society (ATS) clinical practice guideline [10] and the most recent European Respiratory Society (ERS) treatment guidelines [13]. For patients who have been diagnosed with pulmonary sarcoidosis and are considered candidates for treatment, the goal is to reduce granulomatous inflammation and prevent the development of irreversible organ damage (e.g., honeycombing and fibrotic lung disease) while avoiding excess toxicity from medications [14].

After expert recommendations using a modified Delphi process (a strategy for developing consensus based on expert opinion) for the treatment of sarcoidosis were published [15], an ERS Task Force committee developed a treatment algorithm with the evidence-based GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology (Fig. 1) [13]. ERS recommendations include glucocorticoids as an initial therapy for sarcoidosis, although severe disease may warrant immunomodulators or biologics; rituximab, Janus kinase (JAK)-inhibitors, and repository corticotropin injection (RCI; Acthar®)
Gel) should be considered on a case-by-case basis [13]. Of the treatments recommended for sarcoidosis, only corticosteroids (e.g., prednisone) and RCI are approved by the US Food and Drug Administration (FDA) for the treatment of symptomatic pulmonary sarcoidosis [9, 16], with limited evidence supporting the use of the other agents. However, evidence links long-term and high-dose corticosteroid use with increased risk of adverse events (AEs) and higher health care utilization costs [17, 18]. The objective of this review manuscript is to provide an overview of the data on the mechanism of action of RCI as it relates to the pathophysiology of sarcoidosis, as well as the clinical data supporting the safety and efficacy of RCI for the treatment of sarcoidosis. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Pathophysiology of Pulmonary Sarcoidosis

Sarcoidosis is characterized by noncaseating granulomas in response to an exaggerated immune response (Fig. 2), with lung granulomas indicating pulmonary sarcoidosis [19, 20]. Although the exact cause of sarcoidosis is unknown, cancer or exposure to mycobacteria or dust may trigger its presentation [6, 21, 22]. Expression of various inflammatory cytokines, including tumor necrosis factor (TNF)-α and
interleukins, lead to the formation of granulomas [19]. Cytokines produced by Th1 cells (e.g., IL-2, IFN-γ) and Th2 cells (e.g., IL-6) are involved in progression to fibrosis [19, 23].

Melanocortin receptors (MCRs) are expressed in cells within granulomas, including macrophages, mast cells, T cells, and B cells [24]. MCRs are seven-transmembrane G-protein coupled receptors that have an anti-inflammatory effect by stimulating signaling pathways that inhibit expression of inflammatory cytokines [25, 26].

**RCI and its Mechanism of Action**

RCI has been used since the 1950s to treat autoimmune and inflammatory conditions [16]. Although RCI is FDA-approved to treat such conditions, it is not approved for use outside the US. RCI is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) analogs and other pituitary peptides [16]. The manufacturing process for RCI converts the initial porcine pituitary extract with low ACTH content into a mixture having modified porcine ACTH and other related peptides.
peptide analogs solubilized in gelatin [16]. A major component in the formulated, complex mixture is N-25 deamidated (N25D) porcine ACTH (1–39) [16].

RCI is an agonist for all five MCRs [16]. MCR agonists are believed to modulate the hyperactive/dysregulated immune response in sarcoidosis [25, 27]. The complex mixture of ACTH analogs and other pituitary peptides in RCI correspond to unique binding and functional activity on MCRs relative to stand-alone synthetic ACTH peptides [28]. In an in vitro study, RCI was determined to be a partial agonist at MC5R and a full agonist at MC1R, MC2R, MC3R, and MC4R [28]. Among the MCRs for which it is a full agonist, RCI has its lowest functional activity at MC2R [28]. Inversely, synthetic ACTH1–24 has its highest activity at MC2R [28]. RCI has higher potency at MC1R, MC2R, MC3R, and MC4R than its major component, N25D-ACTH1–39, as well as than ACTH1–24, which highlights this mixture’s unique properties.

The anti-inflammatory effects of RCI were initially thought to be mediated indirectly through endogenous corticosteroid production following the engagement of MC2R on adrenocortical cells [29]. However, in animal studies, RCI induced significantly lower corticosterone levels than synthetic ACTH1–24, consistent with their respective functional activity at MC2R [28]. Pharmacologic studies in healthy human subjects have also demonstrated that RCI induces lower cortisol production than does synthetic ACTH1–24 depot at clinically relevant doses, further supporting that RCI has a unique mechanism of action [30, 31]. The lower cortisol response of RCI was achieved despite plasma concentrations of the pharmacokinetic marker of RCI (N25-deamidated porcine ACTH1–39) being higher than concentrations of ACTH1–24 [31].

Recent studies suggest that RCI may predominantly function through direct binding and activation of MCRs on other cell types (Fig. 3). RCI has been shown to directly modulate immune cells and various other cell types via interaction with MC1R, MC3R, MC4R, and MC5R [28, 32–34]. In vitro studies of stimulated human B cells isolated from blood [33], and spleen lymphocytes obtained from a murine model of systemic lupus erythematosus [35] have shown that RCI inhibits proliferation of B cells and antibody production [33, 35]. A study using a mouse model of multiple sclerosis suggested that RCI may shift pro-inflammatory Th1 cells to a more regulatory Th2/Treg phenotype [36]. Alveolar macrophages are activated and release TNF-α in bronchoalveolar lavages of patients with sarcoidosis, especially in those with worsening disease [37, 38].

Further understanding of MCR agonist mixtures such as RCI may be informed by research on individual MCR agonists including ACTH, α-melanocyte-stimulating hormone (α-MSH), β-melanocyte-stimulating hormone (β-MSH), and γ-melanocyte-stimulating hormone (γ-MSH) [25]. α-MSH acts through MC1R to reduce pro-inflammatory cytokines, as shown in a model of peripheral blood mononuclear cells derived from patients with confirmed treatment-naive sarcoidosis [27]. This effect may be achieved by inducing phosphorylation of cyclic adenosine monophosphate-response element binding protein (CREB), as anti-inflammatory effects of α-MSH were blocked by phospho-CREB inhibition [27]. β-MSH and γ-MSH have been studied less extensively, but β-MSH also binds to MC1R, MC3R, and MC4R; γ-MSH binds with low affinity to MC1R and MC4R and with similar binding affinity as other MCR agonists to MC3R [25]. MCR binding leads to activation of each receptor and subsequent inhibition of inflammation [25].

Anti-inflammatory effects of MCR agonists have been demonstrated in preclinical studies of pulmonary disease, including in an in vitro model of human sarcoidosis (challenged peripheral blood mononuclear cells from patients with sarcoidosis), which showed that RCI significantly reduced granuloma-associated increases in the inflammatory cytokines IL-1β, IL-4, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [39]. Melanocortin peptides diminished airway inflammation through activation of MC3R and subsequent inhibition of TNF-α in a model of non-allergic pulmonary inflammation [40]. The MSH analogue STY39 reduced pro-inflammatory cytokines and attenuated pulmonary fibrosis in a murine model [41].
immunomodulatory effects of RCI and related compounds via MCRs likely mitigate the pathophysiology of pulmonary sarcoidosis.

**Clinical Efficacy and Safety of RCI in Pulmonary Sarcoidosis**

Multiple studies have examined the safety and efficacy of RCI for sarcoidosis, with initial reports of efficacy in 1952 [42]. As with most drugs used for the treatment of sarcoidosis, the efficacy of RCI in patients with pulmonary sarcoidosis is mainly based on retrospective data. A retrospective pilot study found that in 29 patients with advanced sarcoidosis who received RCI for 6 months or more, 11 showed improvements, 16 remained stable, and two relapsed [43]. RCI was well tolerated in two-thirds of patients [43]. RCI also showed steroid-sparing effects; most patients were able to reduce their prednisone dose by > 50% (Fig. 4) [43].

A single-blind prospective study of 18 patients with chronic pulmonary sarcoidosis found that in the 16 patients who completed the study, RCI treatment was prednisone-sparing and associated with significant improvements in pulmonary function, chest imaging results, and patient-reported outcome measures over a 24-week period [44]. RCI 40 U was not inferior to RCI 80 U but was more tolerable [44]. Only one patient discontinued treatment due to adverse events [44]. RCI allowed most patients to decrease prednisone dose by > 50% (Fig. 4).

In further support of the safety and efficacy of RCI, a retrospective analysis of medical records for 302 patients with advanced symptomatic sarcoidosis found that RCI was a favorable treatment option [45]. According to physicians’ assessments of change in patients’ health status after RCI therapy, overall status improved in 95% of patients, overall symptoms in 73%, lung function in 38%, and inflammation in 33% (Table 1) [45]. Overall use of concomitant medications decreased by 75% and use of corticosteroids declined by 79% from the 3 months before RCI use to 3 months after RCI use (Fig. 4) [45]. Mean corticosteroid dose decreased from 18.2 mg/day at baseline to 9.9 mg/day after 3 months of RCI use [45].

In a case study, RCI was successful in treating advanced sarcoidosis in a patient who experienced an autoimmune reaction to infliximab [46]. Sarcoidosis skin lesions, including lupus pernio, improved with RCI treatment, which was well tolerated in this case study [46].

An ongoing phase 4, multicenter, randomized, double-blind, placebo-controlled exploratory study (PulSAR) to assess the efficacy and safety of RCI in subjects with pulmonary sarcoidosis should provide additional evidence to further demonstrate the role of RCI in the management of sarcoidosis (ClinicalTrials.gov identifier: NCT03320070) [47]. In this trial,
participants receive RCI or placebo subcutaneously twice weekly for 24 weeks; those receiving placebo will have the opportunity to receive RCI in the open-label extension period [47]. A composite score called the Sarcoidosis Treatment Score (STS) was previously developed.
to capture multiple facets of pulmonary sarcoidosis, which addresses an unmet need identified by a World Association of Sarcoidosis and Other Granulomatous disease (WASOG) task force [48]. Key outcomes in PulSAR include changes in elements of the STS, such as forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO), high-resolution computer tomography (HRCT), King’s Sarcoidosis Questionnaire (KSQ), Fatigue Assessment Score (FAS), and corticosteroid taper [47, 48].

**Therapeutic Options for Pulmonary Sarcoidosis**

Corticosteroids are typically the mainstay of treatment for patients with symptomatic sarcoidosis [12, 15]. Although corticosteroids have been shown to improve chest X-rays over 3–24 months, there is little evidence of an improvement in lung function with these drugs [49]. Systemic therapy (usually corticosteroids) within the first 6 months of diagnosis is strongly associated with continued use 2 years later [50]. There are limited data beyond 2 years to indicate whether oral steroids have any modifying effect on long-term disease progression [49]. Long-term treatment with corticosteroids is associated with an increased risk of AEs [17] and a high rate of clinical relapse [51]. Corticosteroids are linked to cardiovascular risk factors and an increased incidence and progression of atheromatous vascular disease [52] as well as deleterious effects on glucose metabolism that can lead to insulin resistance and complicated diabetes [53, 54]. Other side effects of corticosteroids include thrush, fluid retention, myopathy, osteoporosis, cataracts, and glaucoma [6].

Methotrexate is the most common antimetabolite used as a second-line therapy; it functions as a folate antimetabolite that inhibits DNA synthesis, repair, and replication [6]. Although methotrexate has been shown to effectively control pulmonary sarcoidosis [38, 55] and may have a steroid-sparing effect [55], there are major safety/toxicity concerns with all antimetabolite agents. Adverse events can include nausea/emaesis, stomatitis, bone marrow suppression, and pneumonitis [6]. Methotrexate has a potential for hepatic and hematologic toxicity and is not recommended for those with renal insufficiency [7]. Relapses have been observed after discontinuation of methotrexate, which suggests that the drug’s effects are suppressive rather than curative [55].

Azathioprine is also used as a second-line therapy, but it has increased risk of infections and potential malignancy [56]. Another therapy utilized for pulmonary sarcoidosis is leflunomide, but it has been associated with peripheral neuropathy [56]. Data for mycophenolate suggests that it may be beneficial for sarcoidosis, although it has primarily been studied for interstitial lung disease [56]. Adalimumab and rituximab are monoclonal antibodies that have shown efficacy for sarcoidosis in early studies [56].

The biological agent infliximab is a monoclonal neutralizing antibody against TNF-α [9]. Small, short-term studies have shown that infliximab effectively reduced sarcoidosis symptoms in patients who were nonresponsive to other treatments [9]. Infliximab may cause varying AEs, including abdominal pain, nausea, diarrhea, dyspepsia, headache, rash, pruritus, pharyngitis, sinusitis, sore throat, and infusion reactions, including severe anaphylaxis [9]. Infliximab also increases the risk of infection and may increase risk of metastasis of known cancers and, in rare instances, autoimmune and demyelinating disease [9]. One study found that 55% of patients with sarcoidosis receiving infliximab eventually discontinued treatment, with allergic reaction being the most common reason [57]. Hazard ratios showed significantly higher likelihood of discontinuing therapy due to infection with infliximab (12.1, p = 0.01) and adalimumab (9.7, p = 0.04) than with RCI [57].

RCI is distinct from corticosteroids, inhibitors of cell activation, proliferation, and migration (e.g., methotrexate, azathioprine, leflunomide, mycophenolate), TNF-α antagonists (e.g., adalimumab, infliximab), and anti–cluster of differentiation (CD)20 antibodies (i.e., rituximab) [56, 58, 59]. In other inflammatory conditions, such as systemic lupus erythematosus, idiopathic inflammatory
myopathies, and rheumatoid arthritis, RCI has been found to be safe and effective for treatment of patients who were nonresponsive to corticosteroids [60–62]. The effectiveness of RCI in patients who are refractory to corticosteroids supports RCI’s unique mechanism of action that is distinct from steroids.

Possible side effects of RCI may include change in glucose tolerance, hypertension, and increased appetite and weight gain [60, 61, 63]. These side effects are consistent with those seen with glucocorticoids [61]; this may be expected considering that endogenous production of cortisol from the adrenal cortex is one of the mechanisms of RCI, albeit at lower levels than observed with other MCR agonists [31]. However, RCI is multi-mechanistic in that it may also cause direct modulation of immune cells, such as B cells and macrophages, independently of steroids [28, 31]. This is supported by a recent systematic review showing distinct AE profiles between RCI and glucocorticoids in the treatment of rheumatoid arthritis [64]. Head-to-head studies are needed to distinguish the safety and efficacy of RCI vs. glucocorticoids in the treatment of pulmonary sarcoidosis.

Unlike methotrexate, infliximab, adalimumab, rituximab, and mycophenolate, RCI is FDA-approved for symptomatic sarcoidosis and has a long-standing history in the treatment of autoimmune and inflammatory disorders [16]. Taking the unique mechanism of action, favorable safety profile, and clinical history into account, RCI is expected to soon become an effective treatment option worldwide [65].

**Expert Opinions on RCI for Treatment of Pulmonary Sarcoidosis**

A panel of experts used a modified Delphi process to agree on a starting dose of 40 U RCI twice weekly for patients with less severe disease and that the drug be continued at a maintenance dose (individualized for each patient) for those who responded, particularly those with chronic refractory sarcoidosis [65]. Concomitant steroids are recommended to be quickly tapered in patients receiving RCI, but concomitant use of immunosuppressive medications can be continued [65]. RCI should be down-titrated or discontinued if severe AEs arise or if management of AEs fail [65]. This panel of experts concluded that most patients with pulmonary sarcoidosis in their practices were started on RCI as a second-line therapy after steroids (Fig. 5) [65].

**Future Directions for Pulmonary Sarcoidosis**

Decisions to treat pulmonary sarcoidosis could be increasingly based on modern techniques such as risk stratification and assessment of biomarkers. The first-line, second-line, and third-line strategies for pulmonary sarcoidosis may be an outdated concept. Perhaps the best option for determining appropriate treatment would be through a personalized medicine approach. Disease and risk characteristics, side effect profiles, and patient preference should be taken into account [58]. Patients with Afro-Caribbean ancestry and women, as well as those with multiorgan involvement, high TNF-α release, and soluble interleukin-2 receptor levels, may have higher risk of mortality and progression of sarcoidosis [6, 37, 66]. Positron emission tomography (PET) scans can also be used to determine who should be treated and to evaluate improvement after treatment with RCI [43].

In the future, biopsied lung tissue could be stained using antibodies specific for cell-surface receptors such as TNF-α receptors, MCRs, or CD20 receptors to guide treatment. Patients with expression of a particular receptor type in their affected lung tissue may be best suited for prescription of a corresponding agonists or antagonist for those receptors. For example, infliximab may be appropriate for patients whose biopsies have high levels of TNF-α receptors, rituximab for patients with enrichment of CD20⁰ B cells, and RCI for those with high levels of MCRs. However, antibody staining for therapeutic use is still in the early stages of research and is not currently used for guiding treatment.
CONCLUSIONS

Many recommended treatments for pulmonary sarcoidosis have shortcomings, including treatment failure, toxicity, and/or high discontinuation rates. Unlike most other therapies, RCI has a long-standing history in treating autoimmune and inflammatory disorders, proven safety and efficacy for pulmonary sarcoidosis and is FDA-approved to treat symptomatic sarcoidosis. A recent expert panel found that in clinical practice, RCI is most commonly used as a second-line treatment after steroids [65]. Individualized consideration of risk–benefit profiles is necessary for considering treatments for pulmonary sarcoidosis, including RCI.

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