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

Mechanism of Action of Purified Cortrophin® Gel (repository corticotropin injection, 80 USP U/mL) in Systematic Dermatomyositis and Polymyositis

Abstract

- This document provides information pertaining to select available evidence supporting the mechanism of action of Cortrophin Gel (repository corticotropin injection USP) in two specific types of myositis: systemic dermatomyositis and polymyositis. The active agent in Cortrophin Gel is porcine-derived adrenocorticotropic hormone (ACTH peptide, amino acids 1-39),[1] which is biologically similar to endogenous, human ACTH,[2] and of the same class as other FDA-approved natural-product[3] and synthetic corticotropins.[4]

Note that this document is for information purposes only. Please refer to the Purified Cortrophin Gel (repository corticotropin injection USP) USPI for full prescribing information. 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.

Introduction

Clinical Background

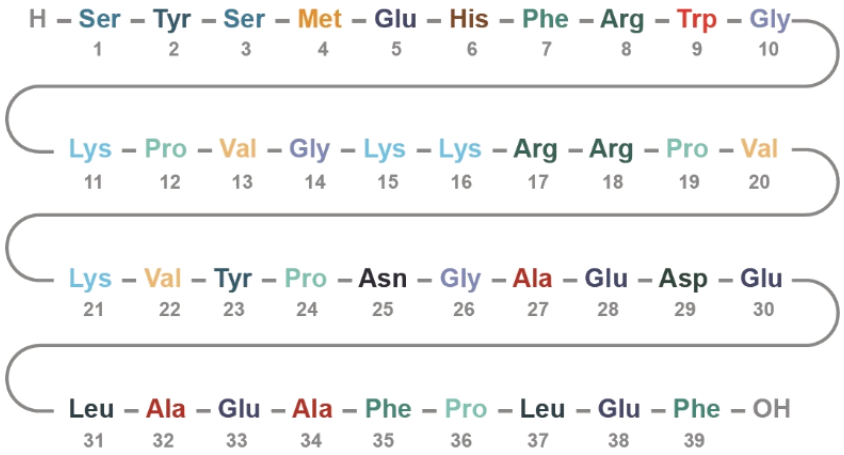
Cortrophin Gel (repository corticotropin injection USP) is approved by the FDA for use in collagen diseases, such as systemic dermatomyositis and polymyositis, two types of myositis.[1]

Composition of Cortrophin Gel

Cortrophin Gel is a porcine-derived purified corticotropin (adrenocorticotropic hormone [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.[1]

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.[1]

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



Mechanism of Action of Cortrophin Gel in Dermatomyositis and Polymyositis

While the precise mechanism of action of Cortrophin Gel is not fully understood, its ability to stimulate glucocorticoid production in the adrenal glands has been well characterized. A growing body of evidence demonstrates that ACTH may supplement the efficacy of glucocorticoid steroids in mitigating dermatomyositis and polymyositis, suggesting Cortrophin Gel may have a nonsteroidogenic component to its mechanism of action.

ACTH is a member of the melanocortin family of peptides that are ligands for the melanocortin receptors, or MCRs, of which there are 5 known isoforms (MC1R-MC5R).[5] These endogenous receptors for ACTH are broadly expressed on cells important to the pathophysiology of dermatomyositis and polymyositis, and are thought to play an important role in the protective and anti-inflammatory effects of ACTH that are not sufficiently explained by ACTH-stimulated adrenal steroidogenesis.[6]

The following sections provide a summary of clinical observations that have led to the exploration of the apparent nonsteroidogenic effects of ACTH in myositis, as well as the preclinical data that help characterize the role of MCRs in potentially mediating these effects.

Clinical Observations in Dermatomyositis and Polymyositis Related to Mechanism of Action

Endogenous, as well as exogenously administered, ACTH stimulates the adrenal production of cortisol, among other glucocorticoids. As many patients with dermatomyositis and polymyositis benefit from glucocorticoid administration, it may be inferred that ACTH may exert its anti-inflammatory effects indirectly, at least in part, by stimulation of steroidogenesis through agonistic binding of MC2R, which is primarily expressed in the adrenal cortex.[6,7] However, some studies with a relatively small number of participants have observed that some patients with dermatomyositis and polymyositis already receiving

corticosteroids have increased clinical benefit from the addition of ACTH, including in patients who did not previously respond to corticosteroids.[6,8–13] Moreover, ACTH allowed many patients to reduce their corticosteroid and other prior medication intake, while maintaining a similar level of benefit, with fewer adverse events.[6,10,11,13–15] Together, these observations suggest that ACTH may possess activity independent of steroidogenesis via the adrenal cortex.

Use of α-MSH as an Analog of ACTH in Preclinical Studies

Preclinical studies interrogating the function of MCRs often use the melanocortin α-melanocyte stimulating hormone (α-MSH), a modified cleavage product of ACTH. With the exception of MC2R, which is selective for ACTH within the adrenal cortex, α-MSH binds and activates all other MCR family members (MC1R, MC3R, MC4R, and MC5R) analogously to ACTH.[5,16] In light of limited preclinical evidence in the context of dermatomyositis and polymyositis, experiments using α-MSH as well as ACTH are used to highlight the potential nonsteroidogenic action of ACTH.

Preclinical Evidence of Nonsteroidogenic Mechanisms of ACTH

Dermatomyositis and polymyositis are types of myositis, which are characterized by chronic skeletal muscle inflammation and muscle weakness, with dermatomyositis presenting with additional skin manifestations.[17,18] Apart from skeletal muscle, and in the case of dermatomyositis, skin, other tissues may commonly be affected, such as lung, joints, gastrointestinal tract, eye, and heart.[18–20] Immune cells that are purportedly driving the pathogenesis of myositis, including muscle-infiltrating T lymphocytes, B cells, macrophages, and other inflammatory cells, as well as target tissues in muscle and skin, are known to express MCRs, suggesting there is potential for a direct, local action of ACTH on these various cell types.[17,21–24] The following paragraphs describe supportive data for the potential direct, nonsteroidogenic actions of ACTH on the pathology of myositis.

A pathologic role of B cells and mature plasma cells has been implicated in dermatomyositis and polymyositis due to the common presence of autoantibodies.[17,24] In a study examining muscle tissue from patients with myositis, increases in mRNA expression of immunoglobulin and B-cell activating factor (BAFF) were found. Both of these proteins can promote maturation of B cells to antibody-producing plasma cells.[25] In isolated peripheral B lymphocyte cell cultures, ACTH was shown to inhibit B-cell proliferation and immunoglobulin G production without affecting their viability, which may suggest the possibility of ACTH acting directly on B cells associated with dermatomyositis and polymyositis pathology.[26]

Isolated cell cultures and animal models of myositis suggest ACTH may have a direct, nonsteroidal effect of reducing inflammation in muscle tissue. In an experimental animal model of myositis, nuclear factor-kappa B (NF-κB) was found to be upregulated in muscle tissue and associated with increased inflammation.[27] NF-κB is a transcription factor that is an important inflammatory mediator associated with pro-inflammatory cytokine release and other immune processes.[28] To support a potential direct, nonsteroidogenic role of ACTH in mitigating this proinflammatory pathway, an in vitro study showed that NF-κB activation by various inflammatory stimuli can be inhibited by α-MSH in isolated human monocytes.[29] Similarly, in human keratinocytes, a type of skin cell, both α-MSH and ACTH (1-39) have

been shown to downregulate NF-κB activation.[22] Collectively, these studies may suggest the potential direct, nonsteroidogenic action of ACTH in myositis.

In murine skeletal muscle, all melanocortin isotypes except MC2R have shown mRNA expression, suggesting ACTH may have a direct action on muscle tissue in a nonsteroidogenic manner.[23] While the effects of melanocortins on muscle are incompletely understood, preclinical studies suggest that melanocortins may increase neuromuscular growth,[30] regulate fatty acid oxidation,[23] and alleviate skeletal muscle injury.[31] In rodents, ACTH has been shown to increase the size of motor endplates, and α-MSH has been shown to increase motor nerve terminal branching as well as motor endplate perimeter and area following neuromuscular injury.[30] Furthermore, MC3R- and MC4R-selective agonists have been shown to prevent muscle wasting and decrease inflammation in arthritic rodent models.[32,33] While not examined in dermatomyositis and polymyositis specifically, these studies using melanocortin agonists that do not bind MC2R suggest the possibility of direct, nonsteroidogenic effects in skeletal muscle.

Conclusion

The broad, anti-inflammatory effects of exogenous glucocorticoid administration have been well documented, and according to clinical reports, steroid-sensitive patients with dermatomyositis and polymyositis can benefit from glucocorticoid use.[34,35] Given the steroidogenic properties of ACTH, control of inflammation through this mechanism is a likely contributing factor in its clinical activity. However, clinical and preclinical data suggest that nonsteroidogenic mechanisms may also contribute to the mechanism of action of ACTH.

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