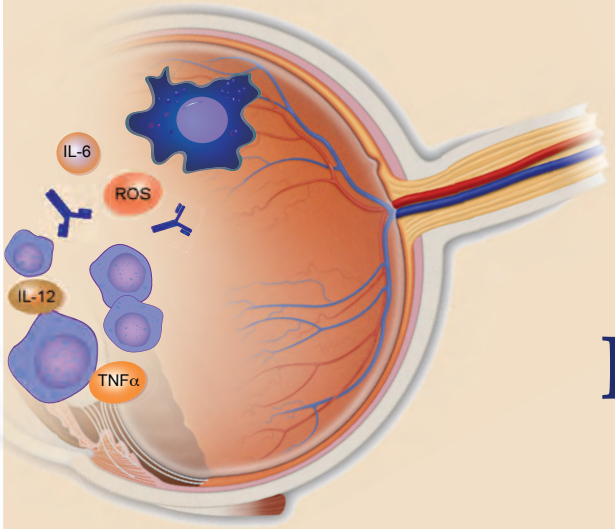

CME Monograph

Melanocortin in the Pathogenesis of Inflammatory Eye Diseases:

Considerations for Treatment

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ACTIVITY DESCRIPTION

Ocular inflammation has the potential to devastate sight if not treated aggressively. The immunopathogenesis is complex, leading to widespread use of broadly immunosuppressive agents, including glucocorticoids. These and newer immunosuppressive agents have variable efficacy in individuals and are associated with serious adverse effects. Recently, the melanocortin pathway has been reconsidered as a treatment target in patients whose disease is refractory to standard therapies, such as steroids and other immunomodulatory agents, or when treatment adverse effects are intolerable. Melanocortins, including the adrenocorticotropic hormone, act upon their receptors to induce multifaceted anti-inflammatory changes throughout the body. Studies have demonstrated that melanocortin treatment can be effective in reducing ocular inflammation due to uveitis and systemic inflammatory diseases, particularly when other approaches have failed. This monograph will review the melanocortin pathway in ocular immunity and therapeutic strategies targeting multiple pathways to reduce inflammation. Several cases and a case series will also illustrate the practical applications of melanocortin receptor activation to reduce inflammation in ocular disease.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe the melanocortin pathway in ocular diseases
- Review mechanisms of inhibition of inflammatory eye diseases
- Identify therapies that target the melanocortin pathway

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Melanocortin in the Pathogenesis of Inflammatory Eye Diseases:

Considerations for Treatment

Introduction

Ocular inflammation arises because of disease processes within the eye or secondary to systemic inflammatory diseases, such as sarcoidosis, multiple sclerosis, rheumatoid arthritis, and Behçet disease. Ocular inflammatory diseases represent a challenge for treating clinicians. Current first-line therapy for ocular inflammatory diseases—namely, glucocorticoids, either local or systemic—is usually effective, but because of adverse effects, the dose needs to be minimized and treatment can become ineffective. Second- and third-line therapies include systemic nonsteroidal immunomodulatory therapies, such as antimetabolites, T-cell/calcineurin inhibitors, alkylating agents, and biologics, all of which can have intolerable immunosuppressive adverse effects and might not be effective in all patients.[1,2] Periods of untreated or undertreated disease lead to chronic inflammation mediated by proinflammatory cells and cytokines, with damage to ocular structures, which can lead to blindness over time. Consideration of alternative treatment targets, such as the melanocortin pathway, can be of value to patients who experience a suboptimal response to traditional treatment or who have intolerable adverse effects from traditional first- and second-line treatments to quickly minimize inflammation and preserve vision. In this review, the melanocortin pathway in ocular health and disease will be explored, with supporting cases demonstrating the clinical use of targeting this pathway for the treatment of uveitis and systemic inflammatory diseases with ocular manifestations.

Role of Melanocortins in Ocular Immunity

Immune privilege within the eye is tightly regulated to protect vision from the effects of chronic inflammation. Ocular immune privilege is achieved through 3 main mechanisms:

- **Maintenance of an immunosuppressive microenvironment:** Pigmented epithelial cells from the iris, ciliary body, and retina secrete immunosuppressive cytokines and form a blood-ocular immune barrier by interacting with immune cells migrating into the eye[3-5]
- **Enhanced systemic tolerance of ocular antigens:** Following ocular inflammation, antigen-presenting cells interact with regulatory T cells to induce durable systemic tolerance[6]
- **Promotion of photoreceptor survival:** Immunosuppressive cytokines promote survival of photoreceptor cells in chronic inflammatory states through suppression of apoptosis and oxidation[7-9]

Aqueous humor contains a wide array of immunosuppressive factors, including the neuropeptide α-melanocyte-stimulating hormone (α-MSH), complement inhibitors, transforming growth factor-β, and Fas ligand.[10-13] α-MSH has been theorized to have a central role in the maintenance of ocular immune privilege.[14] The melanocortin family includes α-MSH, adrenocorticotropic hormone (ACTH), β-MSH, and γ-MSH. These are highly conserved neuropeptides, with diverse cellular targets and effects ranging from inflammation to exocrine secretion, appetite, and behavior.[15] Activation of melanocortin receptors (MCRs) by α-MSH plays a critical role in ocular immune homeostasis. This was demonstrated through resolution of disease in an animal model of uveitis by induced expression of α-MSH that was dependent on MC5R expression.[6] α-MSH activates MCRs on helper T cells (T_H1 and T_H17), macrophages, and microglia to promote conversion to an immunosuppressive phenotype[16,17] and stimulates antigen-presenting cells to promote tolerance to ocular autoantigens in the spleen following inflammation.[6] α-MSH also promotes retinal photoreceptor survival directly through modulation of inflammatory cytokine levels **(Figure 1)**.[7,8,18]

Melanocortin receptor subtypes (MC1R-MC5R) have differential expression throughout the body, which contributes to the wide range of downstream effects **(Table 1)**.[6,15,18-23] ACTH and α-MSH bind all 5 receptors with varying affinity, but ACTH is the only melanocortin that binds MC2R, which induces hormone release and steroidogenesis in the pituitary gland and adrenal cortex, respectively. Systemic treatment with ACTH does not induce steroidogenesis to the same degree as treatment with glucocorticoids, suggesting that activation of other MCRs by ACTH plays a role in fine-tuning the response.[24-27] On the basis of this observation, it has been postulated that treatment of inflammatory diseases with ACTH will not result in the same adverse effects commonly seen with glucocorticoids,[28] but few head-to-head studies have been conducted in adults. ACTH causes release of cortisol from the adrenal gland; thus, the package insert for repository corticotropin injection (RCI) indicates that treatment can cause adverse reactions similar to those caused by glucocorticoids, such as fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.[29]

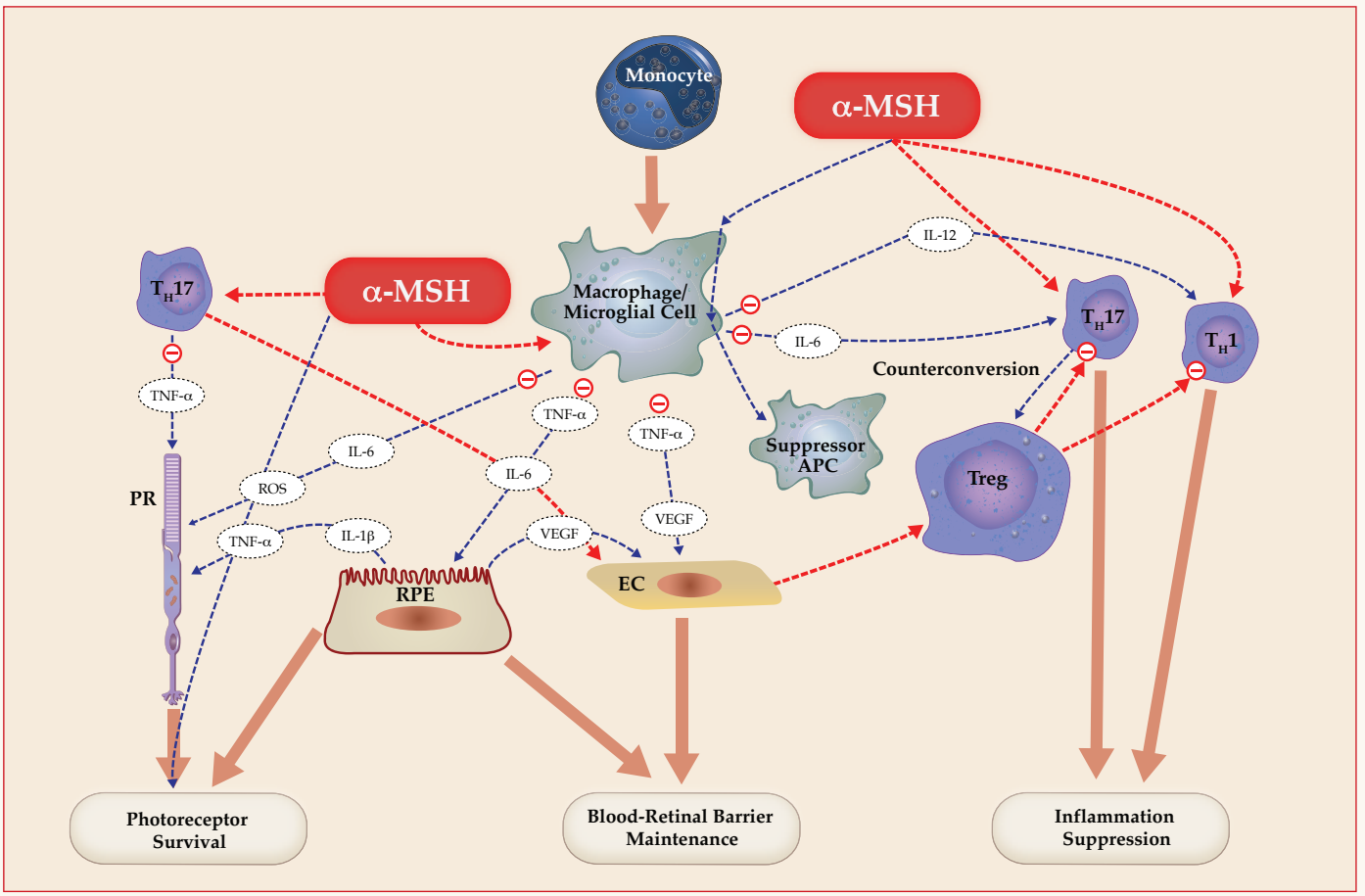

Figure 1. Role of α-MSH in ocular immune regulation

Abbreviations: α-MSH, α–melanocyte-stimulating hormone; APC, antigen-presenting cell; EC, endothelial cell; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-12, interleukin-12; PR, photoreceptor cell; ROS, reactive oxygen species; RPE, retinal pigment epithelial cell; T_H, helper T cell; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

Adapted from *Ocular Immunology and Inflammation*, 25, Clemson CM, Yost J, Taylor AW, The role of alpha-MSH as a modulator of ocular immunobiology exemplifies mechanistic differences between melanocortins and steroids, 179-189, Copyright 2017, with permission from Elsevier.

Table 1. Distribution and Function of Melanocortin Receptors[6,15,18-23]

Melanocortin Receptor	Tissue/Cellular Distribution	Function
MC1R	• Immune/inflammatory cells • Keratinocytes • Endothelial cells • Glial cells • Melanocytes	• Antipyretic/anti-inflammatory • Pigmentation
MC2R	• Adrenal cortex • Pituitary gland	• Steroidogenesis
MC3R	• Dendritic cells • T cells • B cells • Macrophages • Monocytes • Hypothalamus • Retina • Retinal ganglion cells	• Anti-inflammatory • Autonomic functions
MC4R	• Central nervous system • Dendritic cells • Retina • Retinal ganglion cells	• Energy homeostasis • Feeding behavior • Sexual function
MC5R	• T cells • B cells • Macrophages • Dendritic cells • Mast cells • Natural killer cells • Exocrine glands • Retina	• Regulation of the immune response • Regulation of exocrine secretion

Table 2. Immunosuppressive Agents Used in Ocular Inflammation[2]

Class	Generic Name
Antimetabolites	Azathioprine
	Methotrexate
	Mycophenolate mofetil
T-cell/ Calcineurin inhibitors	Cyclosporine
	Tacrolimus
Alkylating agents	Cyclophosphamide
	Chlorambucil
ACTH analogues	Repository corticotropin injection
Biologics	
TNF inhibitors	Infliximab
	Adalimumab
Lymphocyte inhibitors	Rituximab
Interferons	Abatacept
	Interferon α-2a
	Interferon β
IL-1 antagonists	Anakinra

Abbreviations: ACTH, adrenocorticotropic hormone; IL, interleukin; TNF, tumor necrosis factor.

Adapted from Hornbeak DM, Thorne JE. Immunosuppressive therapy for eye diseases: effectiveness, safety, side effects and their prevention. Immunosuppressive therapy for eye diseases: effectiveness, safety, side effects and their prevention. *Taiwan J Ophthalmol*. 2015;5(4):156-163.

Treatment Strategies for Ocular Inflammation

When ocular immune homeostasis is perturbed and immune tolerance is lost, an inflammatory cascade can be triggered that results in infiltration of adaptive and innate immune cells. In posterior uveitis, direct damage to photoreceptor cells by inflammatory immune cells causes loss of vision,[30] whereas in anterior and intermediate uveitis, damage to the iris or ciliary body and increasing opacity in the aqueous and vitreous humor drive vision loss.[3,31] In ocular inflammation due to systemic diseases such as sarcoidosis, infiltrating immune cells in the eye and optic nerve involvement can each contribute to vision loss.[32] Although no unifying mechanism for ocular inflammatory diseases has been conclusively identified, evidence suggests that helper T cells play an important role.[33-36] Ocular inflammation has been successfully treated with both local and systemic glucocorticoids, but long-term systemic use is associated with a number of adverse effects on multiple organ systems.[37] Consequently, use of corticosteroid-sparing therapies is encouraged.[37]

Nonsteroidal systemic immunomodulatory approaches are recommended for persistent or severe inflammation that is sight threatening or when glucocorticoids are contraindicated because of intolerance or treatment failure.[2] These approaches include mycophenolate mofetil, tacrolimus, cyclosporine, azathioprine, and methotrexate **(Table 2)**.[2] Biologic nonsteroidal therapies include adalimumab, infliximab, and interferons α-2a and β.[2,38-40] Corticosteroid-sparing treatments for ocular inflammation are not without risk, and are associated with adverse effects, including infection, secondary autoimmune disease, and malignancy.[37]

Repository Corticotropin Injection

Recently, there has been renewed interest in using an ACTH analogue in cases of nonresponse to immune modulators and corticosteroids or intolerance to adverse effects associated with these agents. RCI is an ACTH analogue that is US Food and Drug Administration approved for use in severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as keratitis, iritis, iridocyclitis, posterior uveitis and choroiditis, optic neuritis, and chorioretinitis.[29] Approval was granted in 1952 and based on safety data only. Although data on efficacy in ocular inflammation are insufficient for inclusion in treatment guidelines or recommendations, a growing number of case reports and small studies show encouraging outcomes for individual patients with challenging ocular and systemic inflammation that is refractory to traditional therapies.[41-47] Mechanistically, data demonstrating reduction in inflammatory cytokine levels observed in patients treated with RCI (eg, interleukin-1 [IL-1], IL-17, and tumor necrosis factor alpha [TNF-α]) support the potential role of RCI as a modulator of helper T cell–mediated inflammation.[48,49]

Cases in the Management of Ocular Inflammation

The following case examples highlight the use of RCI and other steroid-sparing therapies in ocular inflammation that is refractory to traditional therapies and in cases in which traditional therapy is contraindicated.

Case: Recurrent Uveitis and Episcleritis
From the Files of David S. Chu, MD

Background. Posterior segment inflammation includes vitritis, intermediate uveitis, pars planitis, retinitis, retinal vasculitis, choroiditis, posterior scleritis, and optic neuritis. Inflammation in the posterior segment can also present as a combination of the preceding, as shown in **Figure 2.**

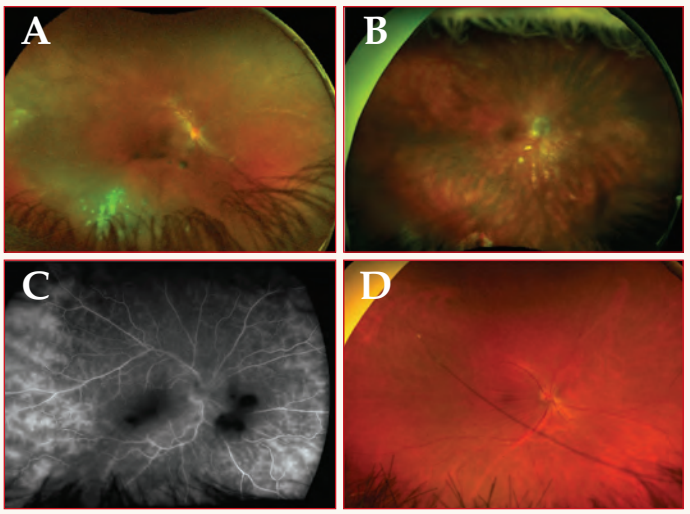

Figure 2. Presentation of posterior segment inflammatory disease. (A) Fundus photography showing vitreous cells and opacities in a patient with intermediate uveitis and retinal vasculitis. (B) Multifocal choroiditis. (C) Fluorescein angiogram showing diffused retinal vasculitis. (D) Choroidal folds in posterior scleritis.

Images courtesy of David S. Chu, MD

Treatment guidelines for uveitis have been developed, and a stepladder approach is recommended for long-term control **(Figure 3)**.[37] The Ocular Immunology and Uveitis Foundation now recommends the introduction of corticosteroid-sparing therapies once inflammation has stabilized; treatment failure is recognized early, with treatment escalation or switching as appropriate. Glucocorticoids are used for control of acute flares, but occasionally, patients become steroid dependent and cannot be tapered from therapy, as illustrated in the following case. Adalimumab is a biologic and the only approved nonsteroidal immunomodulatory agent for use in posterior noninfectious uveitis.[50] In 2 randomized controlled trials, a reduced time to treatment failure was observed vs placebo.[39,40] Serious adverse events judged by investigators to be related to the study drug included infection and allergic reaction. In a study of 31 patients, a response rate of 68% was observed, with 39% of patients experiencing a durable response.[51]

Case. A 61-year-old white female presented with recurrent bilateral uveitis and episcleritis. Anterior chamber reaction and intermediate uveitis has been recurrent for the past 12 years. No history of major systemic illness was found that could be contributory to her disease. Her blood workup was notable for human leukocyte antigen B27 positivity, which confers

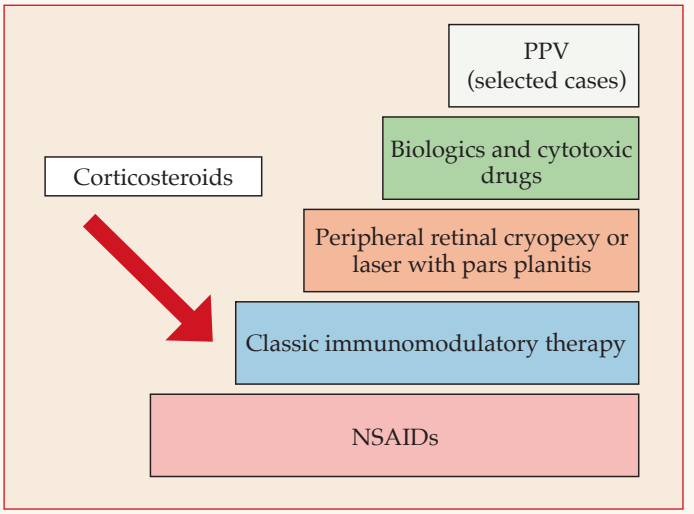

Figure 3. Stepladder approach to uveitis treatment

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PPV, pars plana vitrectomy.

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an elevated risk of certain inflammatory diseases, but was otherwise unremarkable. As a result of chronic inflammation and long-term topical and systemic steroid use, she developed bilateral epiretinal membranes and posterior subcapsular cataracts. At the time of presentation, she was dependent on a daily dose of 10 to 20 mg of oral prednisone and topical prednisolone acetate, 1%, taken from 1 to 4 times a day.

To taper the patient off corticosteroids and alleviate adverse effects, treatment with several nonsteroidal immunomodulatory agents was attempted sequentially. The patient developed debilitating fatigue with methotrexate, had no response to mycophenolate mofetil, developed a hypersensitivity reaction to infliximab, and had no response to adalimumab. The patient was then enrolled in the EYEGUARD-C trial investigating gevokizumab, an IL-1 inhibitor. In this phase 3 trial, 281 participants with noninfectious intermediate, posterior, or panuveitis currently controlled with systemic treatment were randomized to receive either gevokizumab or placebo subcutaneously for 168 days.[52] After 3 months in the trial, she experienced a flare and was transitioned to the open-label study arm. Her disease then became controlled and remained controlled for the duration of the clinical trial. After conclusion of the trial, the patient had bilateral cataract surgery and began experiencing persistent uveitis. She was placed back on 60 mg of prednisone and was subsequently tapered to a dose in the 10- to 20-mg range and low-dose (15 mg) methotrexate to avoid excess fatigue, but had weight gain resulting from use of the steroid.

After discussing several options, including cytotoxic agents, pars planitis vitrectomy, and RCI (the only

Table 3. Effectiveness of Immunosuppressive Therapies for Ocular Inflammation

Medication	Disease Control Within 1 y, %	Corticosteroid Sparing Within 1 y, %	Both Achieved at 1 y, %	Rate of Remission
Methotrexate[54]	66	58	58	8% at 1 y
Azathioprine[55]	62	9.5-47	47	0.09/person-year
Mycophenolate mofetil[56]	73	55-82	55	—
Cyclosporine[57]	52	36	36	0.08/person-year
Cyclophosphamide[58]	76	61	61	0.32/person-year 63% by 2 y 75% by 3 y
Chlorambucil[59]	—	—	—	77% by 4 y
Tumor necrosis factor inhibitors[60]	—	—	75	—

remaining therapy that was approved by the US Food and Drug Administration at the time), the patient was placed on 80 U of RCI administered subcutaneously twice weekly. During a subsequent taper of prednisone and methotrexate, she experienced 1 mild iritis flare, but remained otherwise stable for the next 2 years. At the most recent visit, best-corrected visual acuity was 20/40 OD and 20/25 OS. Prednisone was successfully tapered to 3 mg daily, and methotrexate was tapered to 7.5 mg daily.

Although most patients with posterior uveitis respond well to first-line corticosteroid-sparing therapies, many do not. In a 160-patient uveitis case series analysis, control of inflammation was achieved with methotrexate therapy in 76.2% of patients.[53] Notably, 13% of patients experienced intolerable fatigue, and 8.1% of patients experienced potentially serious adverse reactions. **Table 3** shows data compiled from retrospective cohort studies and a case series on the percentage of patients with disease control and corticosteroid-sparing success with various therapies.[54-60] These data and the case presented herein highlight the importance of individualizing treatment for patients with uveitis according to response and treatment tolerability.

Ocular Inflammation Secondary to Systemic Disease

Several systemic inflammatory conditions can have ocular involvement that threatens sight. These include[31]

- Ankylosing spondylitis
- Psoriasis
- Reactive arthritis
- Rheumatoid arthritis
- Sarcoidosis
- Ulcerative colitis
- Multiple sclerosis

Ocular manifestations can be varied and include optic neuritis, uveitis, and keratoconjunctivitis sicca (dry eye disease [DED]). Ocular inflammation can occur years after diagnosis of a systemic inflammatory condition or, as in the case discussed subsequently, visual changes and associated inflammation can be the first symptom. The American Academy of Ophthalmology Preferred Practice Pattern guidelines for dry eye, optic neuritis, and sarcoid uveitis indicate that treatment might include short courses of corticosteroids to control inflammation, but patients should be monitored for elevated intraocular pressure and cataract formation.[32,61,62] As noted previously, first- and second-line therapies are not effective in all patients, and alternative treatments such as RCI can be considered in those cases.

Case: Optic Neuritis

From the Files of Robert C. Sergott, MD

A 36-year-old presented with a chief complaint of binocular, oblique diplopia. The patient reported having felt dizzy while driving 1 month prior, with tilted images that "just didn't seem right." This aberration was resolved upon tilting of the head to the left. The patient did not have any vision loss or trauma, but did report a 6-week-long episode of visual color and contrast changes 4 months prior and left-sided paresthesias lasting < 5 seconds. The patient denied any exposure to infectious disease; recent travel; or insect or animal bites. His personal and family history was not significant for any potentially contributing medical conditions. Thyroid function and complete blood cell count test results were normal. All ocular examination findings were normal, with the exception of ocular motility test results, which revealed impairment in the ability of each eye to look up and out. Fundus examination revealed mild temporal pallor OS and a cup-to-disc ratio of 0.3 OD and 0.25 OS. The vitreous contained 1+ cells OS. Magnetic resonance imaging (MRI) of the orbits was recommended to investigate the etiology of diplopia. A chest x-ray was performed to investigate potential systemic causes of inflammation. Initial bloodwork test results—including interferon-γ release assay, Lyme disease titer, rapid plasma reagin, serum angiotensin-converting enzyme, anti-nuclear antibody, and chest x-ray—were all within normal limits or negative. MRI showed patchy abnormal pachymeningeal and leptomeningeal enhancement involving the posterior fossa, brainstem, and vermis of the cerebellum **(Figure 4)**. Bulky lymphadenopathy

of the parotid glands was also observed, suggestive of neurosarcoidosis.

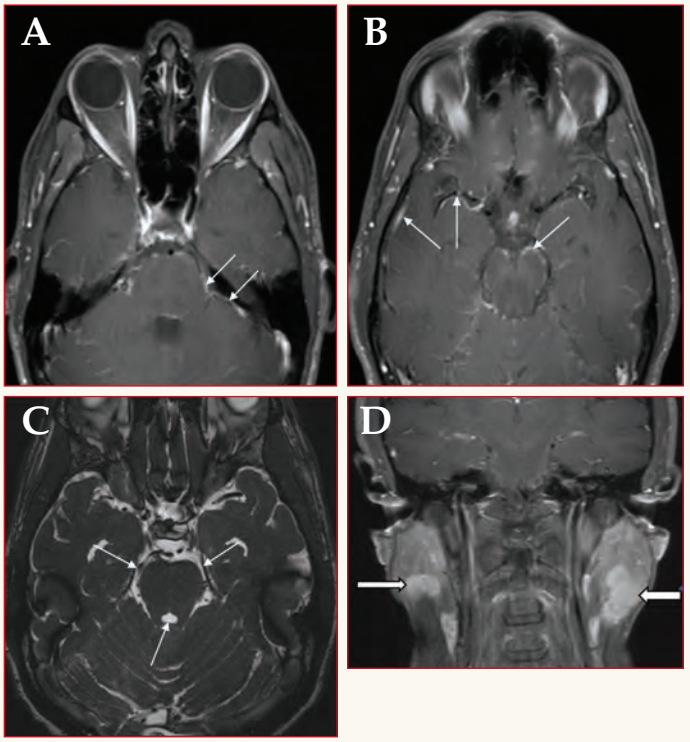

Figure 4. Magnetic resonance imaging scans showing (A-C, arrows) pachymeningeal and leptomeningeal enhancement in the posterior fossa, brainstem, and vermis of the cerebellum. (D) Bulky lymphadenopathy of parotid glands (arrows).

Images courtesy of Robert C. Sergott, MD

To investigate possible sarcoidosis and to rule out tuberculosis and lymphoma, a second opinion was sought regarding the chest x-ray. After examining the original x-ray, the second chest radiologist reported mild bilateral hilar and right paratracheal adenopathy and a subtle micronodular pattern localized mainly in the upper lobes, typical of stage 2 sarcoidosis with pulmonary granulomas **(Figure 5A)**. A chest computed tomography scan was performed, which showed multiple enlarged lymph nodes in the mediastinum and hila and multiple tiny pulmonary nodules distributed in a pattern typical of sarcoid **(Figure 5B)**. Lymph node biopsy showed changes consistent with a reactive lymph node, but were negative for lymphoma.

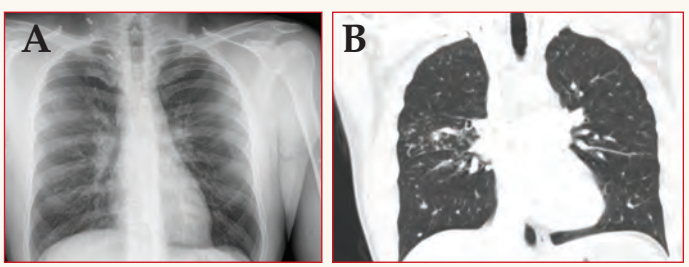

Figure 5. (A) Chest x-ray demonstrating mild bilateral hilar and right paratracheal adenopathy, with subtle micronodular pattern in the upper lobes. (B) Chest computed tomography scan showing enlarged lymph nodes in the mediastinum and hila and pulmonary nodules.

Images courtesy of Robert C. Sergott, MD

On the basis of symptomology and MRI, x-ray, and computed tomography scan findings, the patient was diagnosed with pulmonary sarcoidosis, lymph node sarcoidosis, and neurosarcoidosis and treated with 80 mg of oral prednisone daily for 2 weeks, but experienced significant circadian rhythm disturbance that affected adherence to medication and follow-up. The patient was transitioned to subcutaneous RCI 80 U daily for 5 days, then 40 U for 10 days, resulting in fewer adverse effects. The patient's disease remained inactive during RCI treatment and the vitritis resolved, so the patient was maintained on 40 U 2 to 3 times a week for 1 month, and was then transitioned to pulse dosing of 40 U daily for 10 days every 1 to 2 months.

Advanced Refractory Sarcoidosis Case Series: A Systemized Approach

From the Files of Robert P. Baughman, MD

Background. Previous studies have investigated outcomes in patients with sarcoidosis treated with systemic immunosuppressive agents, including methotrexate and anti-TNF therapies, and RCI. In a 2012 retrospective review of 281 patients taking methotrexate for ocular sarcoidosis, more than 40% required concurrent prednisone, and 25 were treated with concurrent anti-TNF agents (infliximab or adalimumab).[63] All 25 patients responded initially to an anti-TNF agent, but only 10 experienced sustained disease control, indicating that a subset of patients requires additional medication trials or combination treatments to achieve disease control. A subsequent retrospective pilot study of 47 patients with advanced sarcoidosis receiving ≥ 1 systemic therapies was published in 2016.[64] Prior or current treatments at the time of institution of RCI were primarily glucocorticoids, methotrexate, azathioprine, and infliximab. Patients receiving 80 U of RCI subcutaneously twice weekly were evaluated for disease improvement and oral glucocorticoid reduction. Eighteen patients (37%) discontinued RCI within 3 months due to cost (4), death (2), drug toxicity (11), or noncompliance (1). The 2 deaths resulted from respiratory infection and were thought to be related to complications of sarcoidosis rather than to RCI treatment. Eleven of the remaining 29 patients (38%) had objective improvement in 1 or more organs that included either reduced inflammation by chest imaging or positron emission tomography scan, > 10% improvement in forced vital capacity, > 50% reduction in skin lesions, or > 50% reduction in central nervous system lesions on MRI. Dose reductions of ≥ 50% were achieved in 24 patients, with subsequent maintenance of stable or improved disease.

Study Design. In the unpublished case series that follows, 15 patients with sarcoidosis involving multiple organs **(Table 4)** and with a treatment history involving steroids and other immunomodulatory agents **(Table 5)** were treated with 40 or 80 U of RCI twice weekly for at

Table 4. Patient Demographics

	Number of Patients
Female/Male	12/3
African American/White	7/8
Ocular manifestation*	
Uveitis	12
Optic neuritis	7
Retinitis	2
Scleritis	1
Orbital	2
Other organ involvement*	
Lung	7
Skin	4
Central nervous system, not optic neuritis	3
Hypercalcemia	4
Liver	2
Other†	2

* Patient might have more than 1 ocular manifestation and organ involved

† One each: spleen, kidney

Table 5. Prior Systemic Therapy

Therapy	Current	Past
Prednisone	13	2
Methotrexate	3	10
Azathioprine	4	5
Leflunomide	3	5
Infliximab	0	10
Adalimumab	0	5
Rituximab	1	3
Cyclophosphamide	0	4

least 3 months. Response to therapy was evaluated on the basis of the following criteria:

- **Improved:** Patients experienced clinically significant eye improvement, with reduction of at least 50% of ocular inflammation by ophthalmic examination
- **Stable:** Patients have no significant target organ improvement, but reduction in glucocorticoid dosage by 50% or more was achieved
- **Relapsed:** Patients experienced worsening of eye disease when prednisone was reduced, and were maintained on initial or higher dose of glucocorticoids

Results. Patients who completed ≥ 3 months of RCI treatment were assessed for disease improvement, stability, or relapse, as described previously. Of the 15 patients who were treated with RCI, 8 experienced improvement, 4 had stable disease, and 3 had relapsed disease **(Figure 6)**. All 3 who relapsed discontinued RCI between 3 and 6 months of treatment. Five patients discontinued

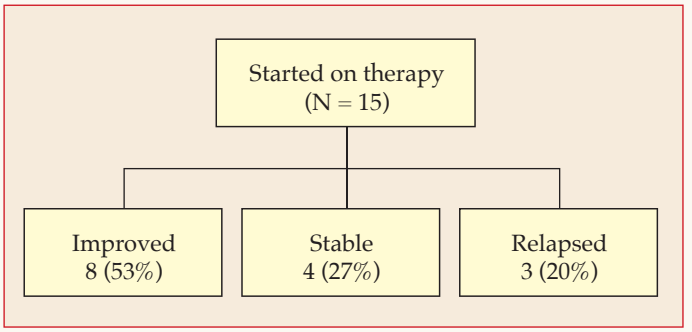

Figure 6. Outcomes with ≥ 3 months' repository corticotropin injection treatment

RCI after 3 months of treatment because of edema (1), itching and nonresponse (1), nonresponse alone (2), or lack of adherence (1). Adverse events were encountered in 10 patients (67%), including edema (6), anxiety (4), itching (1), and worsening diabetes (1) **(Table 6)**. Seven patients underwent a dose reduction of RCI from 80 to 40 U twice weekly by the end of the study.

Table 6. Adverse Events

Adverse Event	Number of Patients (%)
Edema	6 (40)
Anxiety	4 (27)
Itching	1 (7)
Worsening diabetes	1 (7)
Total	10 (67)*

* Two patients had more than 1 adverse event

Commentary. Given that 5% of patients with ocular sarcoidosis require third-line therapy, including anti-TNF agents, and given that more than half of these patients discontinue anti-TNF treatment because of lack of insurance coverage or toxicity, RCI has become an attractive alternative third-line treatment.[63] As shown in this and a previous case series, more than half of patients with advanced treatment-refractory sarcoidosis are successfully treated with 40 or 80 U of RCI twice weekly.[64]

Case: Corneal Inflammation
From the Files of Francis S. Mah, MD

Background. A number of systemic inflammatory diseases, including rheumatoid arthritis and Sjögren syndrome, have DED as an ocular manifestation, which can cause visual morbidity, including blindness, and multiple studies have documented drastic effects on quality of life.[65] Classic characterization of DED has historically focused mainly on tear deficiency and excessive tear evaporation causing damage to the ocular surface and discomfort.[66] More recently, the important role of inflammation as part of the pathophysiology of DED has been increasingly appreciated, although it is thought to be neither necessary nor sufficient for disease development.[66] In rheumatoid arthritis–associated DED

(also known as secondary Sjögren syndrome), T cells, B cells, and macrophages all infiltrate affected tissues. In particular, the role of T_H1 and T_H17 cells is increasingly appreciated.[36] Given the role of melanocortins in the conversion of helper T cells to regulatory T cells, it stands to reason that RCI might modulate disease activity in secondary Sjögren syndrome.

Case. A 54-year-old African American woman was referred for severe filamentary keratitis, with a chief complaint of foreign body sensation that felt "like razor blades." Corneal scarring was evident by direct examination and fluorescein staining **(Figure 7)**. She had a longstanding history of rheumatoid arthritis and was systemically stable on infliximab. She had a long history of using palliative over-the-counter artificial tears. She has been prescribed cyclosporine ophthalmic emulsion, 0.05%; lifitegrast ophthalmic solution, 5%; and a variety of topical steroids, such as loteprednol etabonate ophthalmic gel, 0.5%, and difluprednate ophthalmic emulsion, 0.05%. The patient was unable to self-administer topical therapy because of the deformation of her hands from the rheumatoid arthritis. She also did not have adequate caretaker support to meet the frequent dosing requirements of topical DED therapies. Safety and efficacy in secondary Sjögren syndrome for a number of different therapies were discussed with the patient, including revisiting topical corticosteroids, cyclosporine, lifitegrast, and the novel choice of RCI.

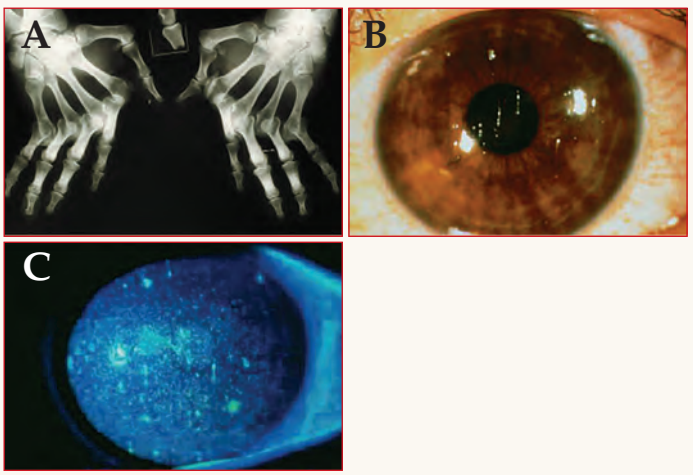

Figure 7. (A) Deformation of hands in rheumatoid arthritis (representative image). (B) Photograph showing corneal scarring. (C) Fluorescein dye staining of the cornea showing extensive epithelial damage.

(A) Reproduced with permission from Clinical Photography, Central Manchester University Hospitals NHS Foundation Trust, UK/Science Source.

(B and C) *Images courtesy of Francis S. Mah, MD*

The patient was started on RCI 80 U daily for the management of corneal inflammation and continued infliximab for systemic management of rheumatoid arthritis and associated ocular disease. Per American Academy of Ophthalmology guidelines for patients treated with corticosteroids for DED, the patient was monitored for increased intraocular pressure and cataract formation.[61] Her corneal disease was adequately maintained after a 2-week period of 80 U daily, with a taper to 30 U/m^2 in the morning for 3 days, 15 U/m^2 in the morning for 3 days, 10 U/m^2 in the morning for 3 days, and 10 U/m^2 every other morning for 6 days.

Conclusion

Ocular disease driven by poorly controlled local or systemic inflammation can be challenging to treat effectively in a corticosteroid-sparing manner. The role of melanocortins in immunosuppression is increasingly recognized. ACTH is hypothesized to act similarly to α-MSH, promoting an immunosuppressive ocular microenvironment and enhanced systemic tolerance of ocular antigens and supporting photoreceptor survival in the face of inflammation by binding to MCRs on circulating immune cells and ocular epithelial cells. The MCR agonist RCI is an ACTH analogue that is rarely used in clinical practice. Small studies and case reports suggest that it can represent a viable option for patients who have refractory disease or who are intolerant of other therapies. Further study is needed to determine the role of RCI in any treatment algorithm for ocular inflammation, but a growing number of studies, including the data summarized herein, support the validity of this approach.

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1. _____ cells are converted to _____ cells upon binding of α-MSH to the MC5R receptor.
   a. Antigen-presenting, regulatory T
   b. Regulatory T, helper T
   c. Helper T, regulatory T
   d. Antigen-presenting, helper T

2. According to animal studies, by which of the following mechanisms has melanocortin treatment been shown to decrease inflammation?
   a. Suppressing the activity of regulatory T cells
   b. Promoting the activity of effector T cells
   c. Increasing IL-1 and IL-17 levels
   d. Suppressing the activity of T_H1 and T_H17 cells

3. Which of the following therapies for ocular inflammation directly targets the melanocortin pathway?
   a. Methotrexate
   b. Repository corticotropin injection
   c. Adalimumab
   d. Rituximab

4. Which of the following therapies for ocular inflammation targets TNF?
   a. Methotrexate
   b. Repository corticotropin injection
   c. Adalimumab
   d. Cyclosporine

5. In the case series presented by Dr Baughman, what proportion of patients previously treated with immunomodulatory agents responded to melanocortin treatment?
   a. None
   b. Less than half
   c. More than half
   d. All

6. Which cell type is thought to contribute to corneal inflammation in DED?
   a. Dendritic cells
   b. Helper T cells
   c. Microglia
   d. Antigen-presenting cells