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Case report

Adrenocorticotropic hormone gel for patients with non-infectious uveitis

Yael Sharon[a,*], David S. Chu[a,b]

[a] Metropolitan Eye Research and Surgery Institute, Palisades Park, NJ, USA
[b] Institute of Ophthalmology and Visual Science, New Jersey Medical School, Rutgers University, Newark, NJ, USA

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ABSTRACT

Purpose: To describe the potential role of adrenocorticotropic hormone (ACTH) gel treatment in patients with chronic non-infectious uveitis.

Observations: We report the clinical course of three patients with bilateral, non-infectious anterior and intermediate uveitis, treated with ACTH gel for ≥12 months. All three patients had chronic and steroid-dependent ocular inflammation with subsequent development of ocular complications. Twice-weekly treatment with subcutaneous 80 unit/day ACTH gel was administered, and clinical outcome measures were observed. After a mean period of 14 months, all patients demonstrated significant improvement in disease activity, stable visual acuity, and an absence of side effects. Systemic steroids dosage was successfully reduced from a mean dose of 16 mg/day upon the initiation of ACTH gel treatment to 2 mg/day at last follow up.

Conclusions and Importance: Subcutaneous ACTH gel has shown to be a safe and effective therapy in the management of non-infectious uveitis. Specifically, ACTH gel plays a role in refractory and steroid-dependent cases and in those who do not respond to or are unable to tolerate other immunomodulatory therapies.

1. Introduction

Uveitis is a group of inflammatory diseases that affect the uveal tract and is classified anatomically, depending on the primary site of inflammation.[1] The clinical course of the ocular inflammation may be acute, recurrent or chronic. Different etiologies are known to be responsible, including infectious and immune-mediated entities, either systemic or limited to the eye. Systemic inflammatory diseases that are associated with uveitis include HLA-B27-associated spondyloarthropathies, Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, Behçet's disease and sarcoidosis, as well as a large number of idiopathic cases.[2] Uveitis is the fifth most common cause of visual loss in the developed world. Vision-threatening complications in patients with uveitis include cataract, glaucoma, and macular edema, among others.[3–5] Chronic non-infectious uveitis requires long term anti-inflammatory treatment. Topical and systemic corticosteroids come with multiple side effects that are not desirable; therefore, in order to minimize their potential risk, the use of immunomodulatory agents is frequently employed, on “off-label” use.[6–8]

Adrenocorticotropic hormone (ACTH) gel is one such immunomodulatory agent. Similar to endogenous ACTH, it stimulates the adrenal cortex to secrete endogenous corticosteroids. Additionally, ACTH gel binds to melanocortin (MC) receptors, in the same way as endogenous melanocortins, which possibly modulates immune cell activation via an extra-adrenal mechanism.[9,10] It has shown efficacy in treating various systemic inflammatory diseases including systemic lupus erythematosus,[12] multiple sclerosis,[13] nephrotic syndrome,[14] infantile spams,[15] dermatomyositis, and polymyositis.[16] However, long-term treatment of uveitis with ACTH gel has rarely been reported.[17–21]

In this case series, we present the clinical course of three chronic, non-infectious uveitis patients, treated successfully with ACTH gel for over a year. ACTH gel (H.P. Acthar® Gel; repository corticotropin injection; Mallinckrodt Pharmaceuticals, St. Louis, MO) at 80 unit/ml dose was administered subcutaneously twice-weekly. Patients were monitored with complete ophthalmologic examinations including visual acuity (Snellen chart), slit-lamp examination, intraocular pressure (IOP) measurement, dilated fundus examination, and when necessary, imaging studies. The degree of intraocular inflammation was graded according to the standardization of uveitis nomenclature (SUN) classification.[1] Patients were also monitored for ocular complications and potential side effects.

1.1. Case 1

A 49-year-old Hispanic man, with a history of uveitis, was referred in October 2014 for worsening symptoms of painless blurred vision,

* Corresponding author.
E-mail address: yael@mersieye.com (Y. Sharon).

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glare, and floaters in both eyes for one year. There was no systemic history of any significant illnesses, and family history was non-contributory. The patient denied previous history of trauma or surgery in both eyes. Serological work up was unremarkable. He was previously treated with methotrexate (MTX) without sufficient control and recurrent flares. MTX treatment regimen was employed according to the acceptable guidelines and considered a treatment failure after at least 3 months of therapy. During his disease course, the patient developed glaucoma, cataract and posterior synechiae in both eyes.

At the time of referral, the patient was treated with systemic corticosteroids (oral prednisone 20 mg/day), topical prednisolone 1% (once daily in both eyes), naproxen (220 mg daily) and intraocular pressure (IOP) lowering agents. On ocular examination, the best-corrected visual acuity (BCVA) was 20/60 in the right eye and 20/40 in the left eye. Slit-lamp examination revealed the presence of keratic precipitates (KP's) in both eyes, 0.5 + cells and 0.5 + flare in the anterior chamber of both eyes, and moderate cataract in both eyes. There was a presence of 0.5 + vitreous cells and haze in both eyes. The cup-to-disc ratio was 0.7 and IOP was within normal limits in both eyes. The patient was diagnosed with bilateral non-infectious anterior and intermediate uveitis, as work-up was unremarkable. Although the patient was relatively controlled on 20mg prednisone, any attempt to taper prednisone resulted in a flare of his uveitis, as well as the development of side effects.

Adalimumab was considered in order to taper systemic corticosteroids; however, the patient's insurance denied adalimumab coverage. The patient was then lost to follow-up and returned to our institute after six months with a flare of his uveitis, following self-discontinuation of treatment. Slit-lamp examination at that time revealed the presence of active KP's in both eyes, 2 + cells in the anterior chamber and 2 + vitreous cells and haze in both eyes. The patient was started on systemic corticosteroids (oral prednisone 60 mg/day) and topical prednisolone (1% every 2 hours) for both eyes. Following initiation of oral corticosteroids, there was an interval improvement in the ocular inflammation.

In July 2015, he was enrolled in a clinical trial (the EYEGUARD™-C study) which evaluated two different doses of subcutaneous gevokizumab, an interleukin-1 beta (IL-1β) inhibitor, for non-infectious uveitis controlled with systemic corticosteroids and immunosuppressive therapy.[22] There was significant improvement with resolution of the vitritis and the anterior segment inflammation in both eyes during treatment with gevokizumab. However, one month after study completion, the patient presented with recurrence of the anterior chamber and vitreous inflammation and was treated with systemic and topical steroids. On ocular examination, the BCVA was 20/70 and 20/40 in the right and left eyes, respectively. Slit-lamp examination showed the presence of active KP's, as well as 0.5 + cells and flare in the anterior chamber of both eyes. On dilated fundus examination, there was the presence of 0.5 + vitreous cells and haze bilaterally. IOP was elevated in the right eye (27 mmHg) and normal in the left eye (17 mmHg).

ACTH gel treatment was initiated in December 2015, along with gradual tapering of systemic corticosteroids. During a 15-month follow-up, the patient was well controlled on ACTH gel treatment with the absence of flares. Oral corticosteroids were tapered down to 5 mg/day at the last follow-up. Fifteen months following initiation of ACTH gel treatment, the BCVA was 20/30 in the right eye and 20/40 in the left eye. Slit-lamp examination revealed no signs of intraocular inflammation. IOP was within acceptable limits. No adverse events from ACTH gel therapy have been observed and the patient lost 170 pounds of weight after discontinuing systemic corticosteroids along with gastric sleeve surgery.

1.2. Case 2

A 36-year-old Caucasian man, first introduced to our institute in April 2012, presented with progressively blurred vision in both eyes. The patient had a history of uveitis for 5 years, as well as glaucoma, and had undergone laser trabeculoplasty in the right eye. The patient was treated in the past with MTX, in a regimen according to the acceptable guidelines, however.

MTX failed to control his uveitis, after at least 3 months of therapy. There was no systemic history of any significant illnesses, and family history was non-contributory. The patient denied previous history of trauma in both eyes. Laboratory evaluation and serology were unremarkable. At the time of referral, the patient was treated with topical prednisolone 1% in both eyes. He was diagnosed with bilateral non-infectious anterior and intermediate uveitis and our work-up was negative.

On ocular examination, the BCVA was hand motion (HM) in the right eye and 20/100 in the left eye, 2 + cells in the anterior chamber of both eyes were noted, as well as extensive posterior synechiae, and cataract in both eyes. The funduscopic exam revealed 4 + vitreous cells and haze in the right eye and 3 + vitreous cells and haze in the left eye. IOP was within normal limits. Sub-Tenon's triamcinolone acetonide injection was given to his right eye and the patient had undergone cataract surgery for visually significant cataract in the right eye.

During the disease course, the patient had persistent ocular inflammation which did not respond to various treatments including voclosporin (as part of a clinical trial) and tacrolimus. On June 2013, he was enrolled in a clinical trial (the STOP-Uveitis study), which evaluated the safety, tolerability and bioactivity of intravenous tocilizumab, an IL-6 inhibitor, for the treatment of non-infectious uveitis.[23] His uveitis was well controlled during the study. Following study completion (May 2014), the patient was not able to obtain intravenous tocilizumab treatment due to denial of coverage by his insurance provider. As another option, adalimumab was also denied for coverage.

The patient had persistent inflammation at that point and, on ocular examination, there were 1 + cells and 0.5 + cells in the anterior chamber of the right and left eyes, respectively. On funduscopic exam, 1 + cells and haze were noted in the vitreous of the right eye, and 0.5 + cells and haze in the left eye. The patient was enrolled in the EYEGUARD™-C study. Two months after the initiation of the study, the patient had a flare that required rescue treatment with systemic corticosteroids (prednisone 80 mg/day) and was converted to open-label study drug dosing, according to the study protocol. The patient later responded to gevokizumab, however, the study was terminated by the sponsor shortly after.

Subcutaneous ACTH gel therapy was initiated on April 2016, while the patient was on 20mg of prednisone. At that time, BCVA was 20/400 and 20/200 in the right and left eyes, respectively. Slit-lamp examination revealed the presence of 2 + cells in the anterior chamber of the right eye and 1 + cells in the left eye, as well as 3 + posterior subcapsular cataract in his left eye. There were 1 + vitreous cells and haze in both eyes and cystoid macular edema (CME) in his right eye. IOP was within normal limits. The ocular inflammation has improved after initiating treatment with ACTH gel and at 6 months' follow-up, there were no inflammatory cells and CME gradually improved. Prednisone was tapered down, until completely stopped after 9 months of ACTH gel treatment. Cataract progression in his left eye required surgery after 12 months of therapy. Following 14 months of treatment with ACTH gel, the patient had been well controlled with no flares and an absence of any adverse events. On ocular examination, the BCVA was 20/150 in the right eye and 20/60 in the left eye, and no intraocular inflammation was noted. IOP remained within normal limits in both eyes.

1.3. Case 3

A 64-year-old Caucasian woman, with a history of uveitis and episcleritis, was referred in January 2011 to our institute, with symptoms of increased floaters in both eyes. On laboratory evaluation, she had positive HLA-B27 antigen. The patient was previously treated with methotrexate, mycophenolate mofetil, infliximab, and adalimumab

unsuccessfully, and in some instances, the patient had developed significant side effects from the medications.

The patient was dependent on systemic corticosteroids (oral prednisone 10–20 mg/day) and topical steroids to control her uveitis.

On ocular examination at presentation, the BCVA was 20/70 in the right eye and 20/200 in the left eye. There were 1 + cells in the anterior chamber of both eyes, as well as 2 + vitreous cells and haze in the right eye and 1 + vitreous cells and haze in the left eye. Epiretinal membrane (ERM) was present in both eyes and IOP was normal. The patient was diagnosed with bilateral non-infectious anterior and intermediate uveitis. Systemic corticosteroids were initiated (oral prednisone 60 mg/day) as well as topical prednisolone acetate (1% every 2 hours) in both eyes.

In order to taper the oral steroidal treatment, the patient was started on adalimumab treatment (40 mg/ml every 2 weeks). However, she experienced recurrence of her uveitis in both eyes, while systemic corticosteroids dose was decreased. In addition, the patient had a vitreous hemorrhage in her left eye that was treated with pars-plana vitrectomy (PPV).

Due to the failure of other immunomodulatory agents, the patient was enrolled in a clinical trial (the EYEGUARD™-C study) in March 2013. After three months from the study initiation, the patient experienced a flare and was transitioned to open-label treatment regimen, and responded well. She completed the study, including an extension period, in August 2015. After completion of the study, the patient had then undergone cataract surgery for visually significant cataract in her left eye. Following surgery, she was on steroid coverage and methotrexate (15 mg weekly), but developed persistent intraocular inflammation that was steroid dependent.

The patient was started on ACTH gel treatment in March 2016. BCVA was 20/50 in her right eye and 20/70 in her left eye. Slit-lamp examination revealed no cells in both the anterior chamber and the vitreous of both eyes. IOP was within normal limits. She was treated at that time with methotrexate (15mg weekly) and prednisone (10mg daily), however developed multiple side effects to treatment. Upon initiation of ACTH gel, methotrexate and prednisone were gradually tapered down, while the uveitis remained controlled. She received ACTH gel for 12 months, with no flares and without the development of side effects. On last follow-up, the BCVA was 20/40 in the right eye and 20/60 in the left eye. There were no signs of inflammation in both anterior and posterior chambers, and IOP was within normal limits. Systemic corticosteroids were tapered from 10 mg/day at the start of ACTH gel therapy, to 3 mg/day at last follow-up and methotrexate dose was tapered to 7.5 mg weekly.

2. Discussion

The clinical use of ACTH gel since the 1950's for various inflammatory diseases has been primarily based on its ability to induce glucocorticoid secretion from the adrenal glands. The extra-adrenal actions of ACTH are the center of on-going research, and the relevance of their therapeutic effect in inflammatory diseases is still not well understood.[9]

ACTH is part of a group of molecules called melanocortins (MCs), derived from the post-translational processing of the precursor proopiomelanocortin (POMC) and endogenously produced in the hypothalamic-pituitary pathway.[24] MCs, such as ACTH and α-melanocyte-stimulating hormone (α-MSH) are expressed during inflammation and have a role as mediators in controlling the inflammatory process.[9,10] They exhibit anti-inflammatory actions by two independent mechanisms; Induction of cortisol production by the adrenal cortex and immune cell modulation via an extra-adrenal mechanism.[25,26] The latter is expressed through inhibition of inflammatory mediators production and cell migration. Examples of such effects are suppression of pro-inflammatory cytokines production (interferon-γ, tissue necrosis factor-α, IL-1, and IL-8), induction of cytokine suppressors (IL-10), inhibition of expression of intercellular adhesion molecules and modulation of lymphocytes activity and proliferation.[24] The anti-inflammatory effects of α-MSH have been demonstrated in a variety of animal models, such as mice, rabbits, and rats.[27–29]

ACTH gel was approved by the United States Food and Drug Administration (FDA) in 1952 for multiple indications, and it is currently being used by rheumatologists, pulmonologists, neurologists and nephrologists to treat various inflammatory conditions across a wide range of approved indications. In ophthalmology, ACTH gel is indicated for inflammatory and allergic ocular diseases. Although the use of ACTH gel for ocular inflammatory conditions has been approved by the FDA since 1952, it did not gain a primary role in ophthalmology. Since other existing therapies in uveitis have multiple shortcomings, including issues with side effects, the need for medication monitoring, high cost and variable clinical response, along with a limited number of FDA approved medications for uveitis management, there has been a renewed interest in ACTH gel.

At the time of the initial approval for ACTH gel, FDA requirements for drug approval merely required evidence that the medication was safe to use in humans. Qualifications for controlled clinical trials and evidence-based data were not part of FDA approval process for new drugs or new indications for an existing drug. The original data, involving ACTH gel approval, included several case reports, describing patients with various conditions treated with ACTH gel who showed clinical improvement. Further drug indications were gradually added based on additional published case reports. Today, the FDA requirements for new drugs and new indications for approved drugs have significantly changed, and the new standards require substantial evidence from well-controlled clinical trials to validate a drug's efficacy and safety. Hence, there is a need for more clinical data on ACTH gel treatment in ocular inflammatory diseases.

Another obstacle is the high cost of ACTH gel. Since long-term therapy is needed in patients with chronic uveitis, this might limit its use as a maintenance therapy in these patients.[30]

In our clinic, ACTH gel is currently reserved for patients who have not responded or who cannot tolerate other immunosuppressive therapies. With all three study patients, their insurance policies covered a major part of the ACTH gel cost, with the rest covered by a patient assistance program. To reduce the use of corticosteroids, particularly in patients with chronic uveitis, we usually introduce immunomodulatory agents in an early stage of the treatment. At the time of initial presentation of our patients, there were no other FDA-approved, non-steroidal immunomodulatory agents (adalimumab was granted FDA approval for specific forms of non-infectious uveitis in 2014), and they were all employed as off-label therapies.

Although ACTH gel prescribing information contains precautions and adverse reactions that are mostly attributed to its steroidogenic effects, its safety profile is significantly better than those of systemic corticosteroids and with an impressive amount of data in its 60 years of use.[11] In our patients, side effects from the steroidogenic action of ACTH gel were not observed.

In this case series of patients with non-infectious uveitis, we presented the long-term clinical course and outcome with ACTH gel treatment. All patients had a bilateral chronic non-infectious anterior and intermediate uveitis, difficult to control, and with persistent inflammation. Table 1 summarizes the patients' demographic data and clinical characteristics. Various therapies, including corticosteroids and numerous immunomodulatory agents, had been tried, with no adequate response and side effects development. During a mean treatment period of 14 months, all patients demonstrated sufficient control of inflammation, stable visual acuity, and no safety concerns. There were no observable abnormalities in complete blood counts, glucose levels, and renal and hepatic function tests of the study patients during follow up on ACTH gel treatment. Furthermore, no significant changes in blood pressure or weight gain were noted. In all patients, therapy with ACTH gel enabled them to taper the corticosteroids dose, while maintaining

Table 1
Patient demographics and clinical characteristics.

Patient No.	Gender, Age (yrs)	Type of Uveitis	Laterality	Etiology	Disease Complications
1	M, 49	AU + IU	OU	idiopathic	Cataract, PS, Glaucoma, CME, ERM
2	M, 36	AU + IU	OU	idiopathic	Cataract, Glaucoma, CME
3	F, 64	AU + IU	OU	HLA-B27	Cataract, ERM, VH

M, male; F, female; Yrs, years; AU, anterior uveitis; IU, intermediate uveitis; OU, both eyes; HLA-B27, human leukocyte antigen-B27; PS, posterior synechiae; CME, cystoid macular edema; ERM, epiretinal membrane; VH, vitreous hemorrhage.

Table 2
Clinical response to ACTH gel in terms of ocular inflammation.

Patient No.	Ocular Findings at Start of ACTH Gel Treatment			Ocular Findings at Last Follow-Up on ACTH Gel Treatment			Concomitant Medications at Last Follow-Up	Treatment Duration (months)
	BCVA (OD/OS)	Anterior Segment Inflammation (0–4+)	Posterior Segment Inflammation (0–4+)	BCVA (OD/OS)	Anterior Segment Inflammation (0–4+)	Posterior Segment Inflammation (0–4+)		
1	20/70; 20/40	+0.5 OU	+0.5 OU	20/30; 20/40	0 OU	0 OU	prednisone 5 mg/day	**15**
2	20/400; 20/200	+2 OD; +1 OS	+1 OD	20/150; 20/60	0 OU	0 OU	none	**14**
3	20/50; 20/80	+2 OS	+0.5 OS	20/40; 20/60	0 OU	0 OU	prednisone 3 mg/day, MTX 7.5 mg/week	**12**

BCVA, best corrected visual acuity; OD, right eye; OS, left eye; OU, both eyes; mg, milligram; MTX, methotrexate.

disease quiescence. The systemic corticosteroids dose was successfully reduced from a mean of 16 mg/day at ACTH gel therapy initiation to 2 mg/day on average at last follow up (Table 2). All patients have had good compliance with therapy and treatment with ACTH gel has been continued for all three patients. However, it is not clear how long will these patients need to be on ACTH gel treatment and if the dose may be tapered over time.

3. Conclusions

Treatment of chronic uveitis is often challenging and requires systemic immunomodulatory therapies as steroid-sparing agents. According to our experience, treatment with ACTH gel is effective for non-infectious anterior and intermediate uveitis. ACTH gel plays a role in refractory and steroid-dependent cases and in patients with ocular inflammatory diseases that do not respond to or are unable to tolerate other immunomodulatory agents. Presenting these case reports may raise awareness of this treatment modality and facilitate further clinical studies of ACTH gel therapy in patients with uveitis.

Patient consent

The study and data accumulation were carried out with approval from the appropriate Institutional Review Board (IRB).

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Conflicts of interest

The following authors have no financial disclosures: Dr. Yael Sharon.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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