Melanocortin Receptors and Their Role in Noninfectious Uveitis: An Expert Panel Discussion

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ABSTRACT

Purpose

The multifactorial nature of noninfectious uveitis (NIU) has left clinicians with a multitude of treatment options, but no ideal treatment. The benefits of topical, subtenon, intravitreal, and oral corticosteroids have been generally recognized, but comparative clinical study data have not been robust. Patients with intermediate, posterior, and panuveitis often require aggressive therapy with systemic corticosteroids, followed by immunomodulatory therapy with anti-metabolites, calcineurin inhibitors, alkylating agents, and biologics. With newer agents available in the armamentarium for uveitis therapy, interpreting data and determining treatment regimens have continued to be open to debate among uveitis specialists and other physicians who manage patients with ocular inflammatory disorders. A melanocortin receptor (MCR) agonist has been approved by the US Food and Drug Administration for a range of severe acute and chronic inflammatory ophthalmic conditions, including diffuse posterior uveitis, but its approval was with minimal clinical supportive data.

Method

An expert panel of US physicians and scientists met via a 2-hour virtual roundtable to discuss several aspects of uveitis management and to prepare a position statement regarding the potential use of MCR agonist in NIU.

Results

This consensus paper covers the known data on MCR agonists, the general organization and practical implementation of MCR agonists in the treatment of ocular inflammatory diseases and uveitis in particular, and offers direction for future clinical study and use.

Conclusion

The MCR class of drugs is showing early promise in a small clinical series of cases in the management of ocular inflammation. Additional clinical data is warranted before an expert panel can recommend the routine use of this class of drugs in the algorithm of therapy for the treatment of NIU.

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INTRODUCTION

Uveitis is a heterogeneous inflammatory disease, with classifications based on anatomic location onset mode and underlying cause (infectious or noninfectious).[1] It is the noninfectious form that is often chronic in nature, and the uveitis is more challenging to control and diagnose. Recurrent inflammation leads to cumulative damage and decreased vision from corneal diseases, cataract, glaucoma, macular edema, vasculitis, and optic nerve inflammation. The SITE study found that 71% of patients were bilaterally affected.[2]

NIU of the posterior segment has been designated an orphan disease in both the United States and European Union. The estimated prevalence of noninfectious uveitis is 121 cases per 100,000 adults and 29 cases per 100,000 children,[3] but some cases can resolve spontaneously. Thus, the true incidence may never be known.[4]

Posterior uveitis accounts for 9.3 to 38% of all cases,[5] and it has often been associated with a number of systemic diseases, including Adamantiades-Behçet's disease, systemic lupus erythematosus, Lyme disease, and sarcoidosis, along with a variety of other systemic autoimmune disorders.[6-15] It is estimated that 5% to 20% of legal blindness in Europe and the United States is caused by uveitis.[16,17] More importantly, this group of patients are normally younger in age than patients afflicted with other vision threatening ophthalmic conditions.

NIU can be driven by a T-cell mediated autoimmune process and perpetuated by pro-inflammatory cytokines.[18-20] Upon presentation, patients often have multiple complaints, with a mean of 3 visual symptoms.[21] Because uveitis tends to affect people between the ages of 20 and 60 years, there is also a loss of productivity as the disease may affect the ability to work.[18,22-24]

Current treatments for NIU range from corticosteroid use (topical and oral), local steroids, immunomodulatory agents, and biologic response modifiers. Topical and local steroid use should be monitored closely and long-term use limited since topical and local steroids can cause cataract and glaucoma.[25-27] Long-term use of systemic corticosteroids can lead to mood swings, hyperlipidemia, weight gain, diabetes, hypertension, and osteoporosis.[21,28] Periocular and subtenon steroid injections have been met with mixed results in the treatment of uveitis, primarily as a result of poor drug absorptions when delivered in this method.[4] Intravitreal depot and sustained release agents are widely used, but they are limited by safety concerns, particularly glaucoma and cataract. Patients often remain on three to four times the recommended maximal dosage of oral corticosteroids for maintenance, with only 12% prescribed immunomodulatory agents to bring corticosteroid use into a target range of 7.5 mg/day.[21]

Immunosuppressive/immunomodulatory agents employed to manage NIU include antimetabolites (azathioprine, methotrexate, and mycophenolate mofetil), T-cell inhibitors (cyclosporine or tacrolimus), alkylating agents (cyclophosphamide, chrorambucil), and tumor-necrosis factor-α (TNF-α) blockers (adalimumab, infliximab), as well as other immunosuppressive or immunomodulation agents, including daclizumab, sirolimus, secukinumab, anakinra, interferon-α, and intravenous immunoglobulin G, the majority of which are used off-label. The only on-label systemic treatments for NIU approved for use in the United States are prednisone and adalimumab. However, the high rate of adverse events leads to a comparable discontinuation rate.[2,29,30]

Biologics (such as adalimumab or infliximab) are recommended by the American Uveitis Society as potential steroid-sparing pharmacologic agents in posterior uveitis, panuveitis, and severe uveitis associated with seronegative spondyloarthropathy.[31] In the pediatric population, the TNF-α class of medications is used as second-line in children refractory to methotrexate, or as first-line treatment in those with severe complicated disease at presentation.[32] While biologics offer a safer profile than corticosteroids,[33-35] a moratorium on intravitreal infliximab use was recommended because of its significant risk of severe panuveitis and vitreous opacification.[36,37]

Adalimumab has been recently approved in the United States for adults with noninfectious intermediate, posterior, and panuveitis. Approval in the European Union includes only those patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.[38]

However, adalimumab is not without its own risks, including a two-fold risk of serious infections, the most notable of which is reactivation of tuberculosis.[39] Deep fungal and other serious and atypical infections can also be promoted by adalimumab, and the biologic has also been associated with worsening or initiating multiple sclerosis and neurological disease.[39]

There are serious side effects associated with the overall TNF-α class of medications, including lymphoma, infections, congestive heart failure, demyelinating disease, drug-induced lupus erythematosus, and induction of auto-antibodies, as well as systemic side effects.[40,41]

Other biologics used off-label (tocilizumab) have shown moderate efficacy in recalcitrant uveitis (n = 10), as control of inflammation and steroid sparing were achieved in 63% and 71% of uveitis patients at 6 and 9 months.[42] In that study, the treatment was not without adverse events, including neutropenia, unacceptable dizziness/nausea, severe angioedema, and severe abdominal pain. Recently, the primary outcomes of the STOP-UVEITIS were reported, demonstrating the benefits of interleukin-6 inhibition in

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reducing vitreous haze and improving uveitic macular edema in patients with noninfectious intermediate, posterior, and pan-uveitis.[43]

The high cost of these agents coupled with the limited long-term safety and efficacy data has prevented biologics from being endorsed as first-line therapy in the treatment of NIU.[44]

There are suggestions in the literature that H.P. Acthar Gel (repository corticotrophin injection) 80 U/mL dosed twice weekly, (concomitantly with prednisone 15 mg a day and azathioprine 100 mg a day) may be successful in cases of sarcoidosis where patients develop a reaction to infliximab.[13] However, the cost of this treatment class is also considered high.

There are other socioeconomic concerns with current treatments for uveitis as well. With about half the patients first presenting in their 30s and 40s, uveitis has a significant socioeconomic impact and an equal negative impact on quality of life.[18,30,45,46]

Compared with a normal-vision reference group and the US general population, NIU results in "meaningful reductions" in mental health outcomes, health-related quality of life, and vision-related functioning.[47] Patients can also develop depression and anxiety, as the uncertainty of when their next episode will happen remains unknown.[18]

The economic impact is similar — in 2011, it was estimated the total annual cost in the United States for people who have gone blind from uveitis was about $240 million, or about the same cost for those who have gone blind from complications of diabetes.[18] The main components of cost are loss of income (23%-43%), burden of care (24%-39%), and paid assistance (13%-29%).[48]

To date, there is some Level 1 evidence to support the use of adalimumab (a biologic) in the treatment and/or maintenance of NIU.[49,50] There are also long-term follow-up outcomes from the Multicenter Uveitis Steroid Treatment (MUST) study that provides Level 1 evidence as well.[51] This may be a result of the heterogeneity of the disease.

NEW AGENTS FOR UVEITIS

Uveitis is not a singular disorder. In certain cases, it is the "manifestation of potential systemic diseases that may have very specific individual therapeutic targets,"[52] or it may be one of many forms of inflammation isolated to the eye. Often, the inflammation is undifferentiated or idiopathic.

MELANOCORTIN RECEPTORS

Melanocortins are endogenous peptides that have been shown to inhibit leukocyte activation and promote inflammation resolution; they may affect behavior, the cardiovascular system, central and peripheral electrophysiological parameters, and food intake; and they may be protective against tissue damage.[53-55]

The literature shows MCRs may induce regulatory immunity against autoantigens that are in the eye; the literature discusses melanocortin protection of retinal cells and expression of MCRs in the retina.[53,56-60]

Melanocortins — adrenocorticotropic hormone (ACTH), α-melanocyte–stimulating hormone (α-MSH, β-MSH and γ-MSH) — are polypeptides derived from a common precursor pro-opiomelanocortin (POMC).[54] To date, five subtypes of MCR have been identified (MC_1 to MC_5), and ACTH can activate all five.[54]

Outside the eye, the effects of α-MSH on expression of cytokines and metalloproteinase suggest a role in the inflammatory and degenerative processes.[58,61] α-MSH activates all known MCRs (except MC_2) and exerts protective effects on retinal vascular endothelial cells.[53]

MC_3, MC_4, and MC_5 are expressed in the inner

neural retinal layers, with MC_3 and MC_4 expression has been found in retinal ganglion cells.[56] MC_1 has been detected in retinal pigment epithelial cells.[61,62]

UNDERSTANDING MCRS

At the cellular level, inflammation is a dynamic tissue response that defends the host against insults from infection, trauma, or damage.[63] To prevent the development of persistent or chronic inflammation, the inflammatory reaction must be entirely resolved to prevent further tissue damage. In the past few decades, researchers have determined the resolution of inflammation is a "carefully managed active process," and deficiency in any one of the components can result in uncontrolled chronic inflammation,[64] not unlike that what occurs in NIU.

Studies have shown that by binding to the MCRs, repository corticotrophin may have both anti-inflammatory and immunomodulatory properties.[65,66] Further, MCR activation has been shown to decrease the activity of T-helper cells and increase the number and activity of T-regulatory cells.[66] The dual mechanism of action of H.P. Acthar Gel provides the potential to treat the acute inflammation, as well as to induce long-term remission in NIU.

MCRS AND OCULAR INFLAMMATORY DISEASE

Repository corticotropin was approved by the US Food and Drug Administration in 1952 for the treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation. This approval was granted with safety data alone. Consequently, there is currently not enough evidence to endorse first-line use of this class of drugs in ocular inflammatory disease, including NIU.

However, inflammatory cells (including lymphocytes, monocytes/macrophages, and neutrophils), as well as tissue-based cells express MCR.[54] The literature confirms ACTH as a steroid-sparing treatment for numerous systemic inflammatory disorders, and it has been found to be more effective than corticosteroids in some studies.[67-69] A recent review of ACTH has suggested new ACTH-like melanocortin drugs devoid of steroidogenic actions (and therefore, side effects) should be developed.[70]

Repository corticotropin is approved for ocular inflammation and ocular inflammatory diseases, and therefore deserves careful evaluation for possible clinical utility in NIU.

Faculty members of this panel are evaluating H.P. Acthar Gel in uveitis, including as twice- or thrice-weekly treatment for NIU. One published case study has suggested it may be a "safe and viable therapeutic option" for NIU and retinal vasculitis.[71] The faculty is in agreement that the clinical efficacy and safety of ACTH gel needs additional study, especially in NIU. There may be potential cost savings with using this class of medications over immunomodulatory agents, especially if long-term control and remission of NIU can be established.

PROPOSED NEXT STEPS

It is this panel's consensus that the evidence published to date warrants increased evaluation of MCRs in ocular-specific cells. The faculty members hypothesize that the mechanism by which MCRs have been proven useful in diseases, such as rheumatoid arthritis and multiple sclerosis, may be duplicated in ocular inflammatory diseases that include NIU. Repository corticotropin is approved for ocular inflammation and ocular inflammatory diseases, and therefore deserves serious careful evaluation for possible clinical

utility in NIU.

However, there are currently no Level 1 randomized clinical trial data for clinicians to evaluate the role of ACTH as a steroid-sparing treatment for NIU. This panel recognizes the difficult undertaking a randomized clinical trial would be in NIU; however, the faculty believes that these types of trials will help clinicians and scientists understand the level of efficacy and better identify "appropriate" patients for various treatments.

Among its numerous indications, H.P. Acthar Gel may be used to treat rheumatic, collagen, dermatologic, allergic, respiratory, and edematous disease states.[72] It is also used to treat autoimmune diseases that have potential ophthalmic manifestations,[7-14] including sarcoidosis[9] and rheumatoid arthritis.[10,11,14,15]

The faculty members also advocate additional post-marketing studies to further confirm the safety and long-term efficacy of this ACTH treatment in NIU. Ongoing studies in both scleritis (the ATLAS Study) and intermediate, posterior, and pan-uveitis (the ACTHAR Study) may yield data to address these queries. Equally important, the long-term data will also help to determine the ability of the MCR agonist class of medications to induce permanent remission of uveitis.

CONCLUSIONS

Additional data are necessary before recommending this class of drugs for the treatment algorithm of uveitis. The expert panel recommends phase 4 post-marketing studies and is cautiously optimistic about the mechanism of action and potential benefits of this class of drugs in the treatment of NIU. At this time, there is not enough evidence to support first-line use of H.P. Acthar Gel over corticosteroids and immunomodulators (as recommended by the American Uveitis Society and other societies and authorities in the field) in specific uveitic conditions. However, there is anecdotal evidence on the mechanism of action of MCRs to warrant consideration as a potential therapy in patients with recalcitrant and chronic ocular inflammatory diseases. ■

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