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FOREFRONT REVIEW

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Uveitis: contrasting the approaches in Japan and the United States

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Abstract

Purpose To compare the approaches to uveitis in Japan and the United States.

Methods This report is based on the author's personal experience, conversations with Japanese colleagues, and a literature search using the database of the US National Library of Medicine.

Results The frequencies of specific forms of uveitis vary between the two countries. Options for therapy are affected by government regulations and the impact of insurance carriers. In both countries, there is a stepwise approach to therapy beginning with topical corticosteroids and ultimately advancing to biologics. Despite the differences, the goals for therapy, disease control with minimal toxicity, are the same.

Conclusions Genetic, environmental, and regulatory differences impact the approach to uveitis. Despite these factors, the goal for therapy is essentially the same.

Keywords Uveitis · Japan · United States · Behcet's disease · Biologics

Introduction

Uveitis, which is synonymous with intra-ocular inflammation, is a collection of diseases that includes a) systemic, immune-mediated diseases like sarcoidosis; b) immune-mediated syndromes confined to the eye like serpiginous choroidopathy; c) infections like varicella zoster; d) masquerade syndromes like lymphoma; and e) adverse reactions to medications such as intravenous bisphosphonates. Despite this broad classification scheme, patients often do not fit clearly into a diagnostic niche and become labelled as having idiopathic disease [1] (which some term undifferentiated [2] or non-classifiable[3]). Although uveitis is uncommon compared to diseases such as cataract, glaucoma, or macular degeneration, it is actually comparable to diabetic retinopathy or macular degeneration in terms of years of visual morbidity [4–7]. In contrast to diseases like diabetic retinopathy which tend to begin near the end of life, uveitis often presents at a much younger age and consequently can cause years of visual loss. Japanese ophthalmologists have made major contributions to understanding uveitis, especially with regard to Vogt-Koyanagi-Harada disease [8], Behcet's disease [9], tubulo-interstitial nephritis with uveitis [10], sarcoidosis [11] and acute retinal necrosis [12]. In this review, I examine how the diagnosis and treatment of uveitis differ between ophthalmologists in Japan and the United States. My understanding of the approach to uveitis in Japan comes from the published literature and conversations with ophthalmologists who treat uveitis in Japan. My understanding of uveitis in the United States is based on my own experience as well as the published literature and discussions with colleagues. This sampling is informative, but it is important to recognize that individuals in either country might differ greatly from what I describe.

Diagnosing uveitis

The prevalence of disease is influenced by environmental and genetic factors. Not surprisingly the frequency of

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specific forms of uveitis differs between Japan and the United States (Fig. 1). A survey of members of the Japanese Ocular Inflammation Society published in 2012 reveals that sarcoidosis, Vogt-Koyanagi-Harada disease, and acute anterior uveitis are the most commonly diagnosed forms of uveitis [13]. A study from the University of California, Los Angeles (UCLA) compared a community-based practice to the referral practice at UCLA [14]. In a community practice in the US, anterior uveitis predominates. In a referral practice, anterior uveitis is less common because it can be usually managed by topical therapy alone and may not require management by a specialist. Despite the reluctance to refer patients with anterior uveitis, in both the community and the referral setting, anterior uveitis is far more common in US compared to Japanese uveitis clinics. In my own clinic, HLA B27-related acute anterior uveitis, often in the setting of a spondyloarthropathy, is the most common diagnosis [15]. Sarcoidosis is less common as an identifiable cause of uveitis compared to Japan, but it does rank second as a systemic disease in association with uveitis. Behcet's disease, Vogt-Koyanagi-Harada disease, and tuberculosis are more common as causes of uveitis in Japan than in the United States, while birdshot retinochoroidopathy is more common in the US. In both countries, idiopathic or unclassified disease account for approximately a third or more of the patients [13–15].

Laboratory testing for the cause of uveitis should be guided by Bayes theorem which states that the treating physician's estimate of the pretest likelihood of a diagnosis should affect how the test results are interpreted. This means that the posttest likelihood of the diagnosis subsequent to a diagnostic test is influenced greatly by the pretest likelihood [16]. In Japan HLA B51 typing is used to support a diagnosis of Behcet's disease, but such typing is rarely if ever used in the United States. In Japan, renal biopsy is used to support a diagnosis of tubulo-interstitial nephritis with uveitis [10], but this approach is rare in the US. However, in many instances, the approach in the United States can be the same as that in Japan. A Japanese study was the first to reveal the value of distinguishing sarcoidosis from idiopathic uveitis by finding that some patients with ocular sarcoidosis also have cardiac sarcoidosis associated with potentially life-threatening arrhythmias [11]. We have made a similar observation in our clinic [17].

Treating uveitis

In both the United States and Japan, most ophthalmologists follow a step wise approach to the treatment of uveitis (Fig. 2). Topical corticosteroids are tried initially, especially for anterior disease. If these prove inadequate and if intraocular pressure is not a rate limiting factor, many practitioners opt for locally injected corticosteroids before selecting oral corticosteroids. Steroid sparing therapy is used in both countries, but the usual choice for a steroid sparing medication differs considerably (see below). Alkylator therapy, which includes cyclophosphamide and chlorambucil, is included in Figure 2. While some literature supports its use [18], alkylator therapy is rarely employed to treat uveitis in either the US or Japan because of its toxicity and the availability of excellent alternatives. In addition, it is important to recognize that the approach in Figure 1 advances from

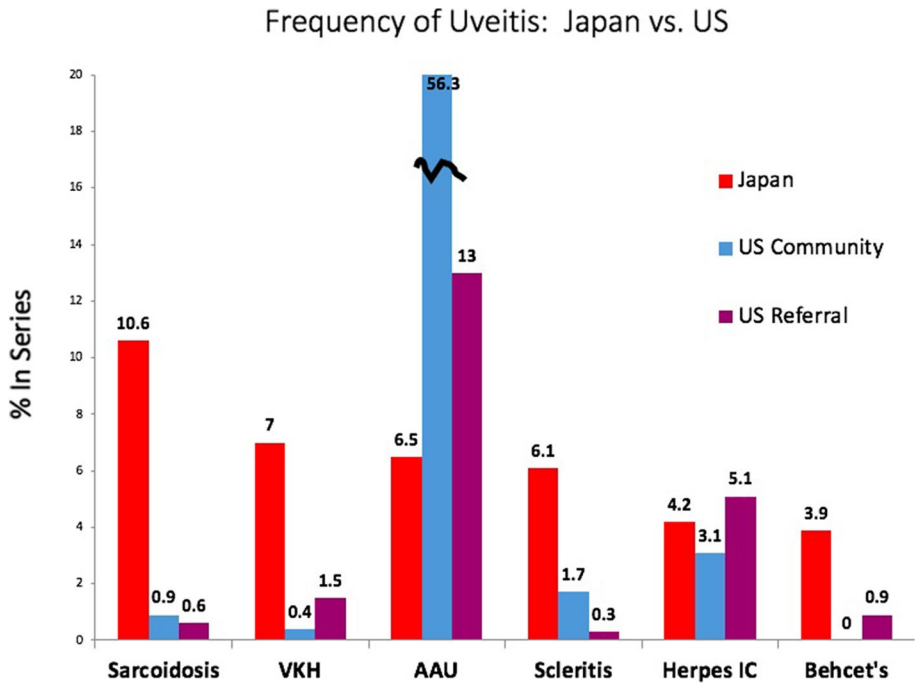

Fig. 1 The frequency of specific diagnoses for subsets of uveitis is compared using a multicenter study from Japan and a US study that includes both a community practice and a university referral practice. The six most common specific diagnoses in Japan are compared to the US clinics. VKH=Vogt-Koyanagi-Harada disease; AAU=acute anterior uveitis; IC=iridocyclitis

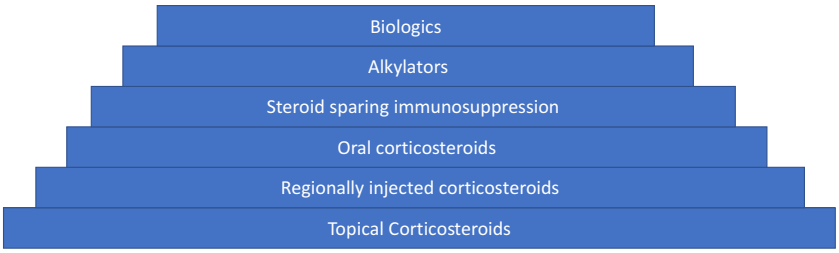

Fig. 2 The stepwise approach to the therapy of uveitis is depicted as accepted in both Japan and the US

relatively safe therapy to potentially more toxic therapy. However, for some diseases and some situations such as Behcet's disease [19] or serpiginous choroiditis [20] threatening the macula, many experts skip directly to immunosuppression such as a biologic for Behcet's or a combination or oral corticosteroids and more than one steroid sparing drug for serpiginous.

The treatment for non-infectious forms of uveitis is influenced by a variety of factors which include the anatomic location of the inflammation, the activity or severity of the inflammation, and to some extent, the specific subtype of inflammation. Treatment is also affected by government regulations which include approval to use a medication for a specific indication. Options to treat uveitis in the United States but not available in Japan include an implant that delivers the corticosteroid, fluocinolone, into the vitreous humor for 30 consecutive months and a topical corticosteroid, difluprednate, which is absorbed trans-sclerally and thus seems to be more effective for macular edema and inflammation posterior to the lens when compared to prednisolone acetate [21]. The topical corticosteroid, betamethasone, is more popular as an option in Japan compared to the US (Okada, A., personal communication). In Japan, infliximab is approved to treat uveitis associated with Behcet's disease. In the US, many medications are used "off label", meaning that once approved for one indication, they are sometimes prescribed for a different indication. For example, if a US physician prescribed infliximab for Behcet's disease, the indication would be off label. However, if the patient has insurance and the medication is expensive, the likelihood is that the insurer will need to approve this usage. This process may require a so called "peer to peer" teleconference in which the prescribing physician discusses the rationale to prescribe a given medication. Obviously, such a teleconference is time consuming and does not always result in a favorable result. Many medications used routinely in the United States to treat uveitis including methotrexate, azathioprine, mycophenolate, cyclosporine, and tacrolimus have not been approved by the US Food and Drug Administration (FDA) for this indication. For diseases like scleritis or orbital inflammatory disease, there are no FDA approved medications, reflecting the dearth of randomized controlled trials for these indications. Recently, multicenter randomized controlled trials, Visual I [22], Visual II [23], and Sycamore [24] have provided data establishing the efficacy of the biologic, adalimumab, for non-infectious intermediate, posterior, or panuveitis and for the anterior uveitis associated with juvenile idiopathic arthritis. Another randomized controlled study, MUST, reports 7 year follow up data comparing the fluocinolone implant to oral immunosuppression with the latter being superior [25]. Several consensus statements provide useful advice about the treatment of uveitis [26, 27], but not all recommended approaches are government approved in Japan.

Although progress is being made in treating uveitis, most commercially sponsored trials include multiple forms of non-infectious uveitis. There is no guarantee that a medication effective for Behcet's disease will have similar efficacy to treat sarcoidosis. The efficacy of type I interferon such as interferon alpha in treating inflammation illustrates clearly that not all forms of inflammation should be regarded as being identical with regard to therapy. Giving alpha interferon is effective in treating Behcet's disease [28], while inhibiting type I interferons are effective in the treatment of systemic lupus [29]. The uveitis community could benefit greatly from studies on specific forms of uveitis comparable to Behcet's disease [19] or for uveitis associated with JIA [24]. Obstacles to achieving this include cost and the relative rarity of each specific entity.

In 2005 Esterberg and Acharya published the results of an informative survey on treating uveitis based on the responses of 45 members of the American Uveitis Society [30]. The survey found that methotrexate and mycophenolate were the two most used medications for anterior, intermediate, or posterior/panuveitis. For inflammation posterior to the lens, physicians often preferred mycophenolate but frequently used methotrexate initially, presumably because the cost is considerably less. While randomized controlled trials have not evaluated methotrexate [31], mycophenolate [32], or azathioprine [33] for multiple forms of uveitis, extensive clinical experience does support their use. The only oral immunosuppressive medication approved in Japan to treat non-infectious uveitis, cyclosporine, ranked as the third or fourth preference in the US survey, depending on which part of the uveal tract was inflamed. Thus, government regulations result in a major difference in how uveitis is treated in comparing the two countries.

Oral corticosteroids have a multitude of toxicities such as weight gain, mood change, hyperglycemia, lowered resistance to infection, and osteoporosis. A post hoc analysis of the Visual I and II studies show that an increased dose of prednisone significantly increased the likelihood of adverse events [34]. Surprisingly, a survey of ophthalmologists in the United States shows that 62% of patients with uveitis were receiving oral corticosteroids at an average dose equivalent to 34 mg/day of prednisone [35], a dose with a high likelihood of side effects.

Although methotrexate is not approved in Japan to treat uveitis, it might be given for an associated illness such as juvenile idiopathic arthritis. When I prescribe methotrexate, I usually start with a dose of 15 mg/week and try to achieve a dose of 20 to 25 mg/week if tolerated. To improve absorption, I often prescribe a subcutaneous formulation. In Japan, doses of 7.5 mg/week are often prescribed. Genetic differences in drug metabolism, differences in average body size, and the microbiome might contribute to the dosage differences between the two countries.

Future treatments

Adalimumab, a monoclonal antibody that neutralizes tumor necrosis factor, has become the first biologic to be approved to treat multiple etiologies of non-infectious intermediate, posterior or panuveitis in both the US and Japan. Additional therapies are under study, although such study is usually initially for the treatment of immune mediated disease other than uveitis. These approaches include other biologics such as monoclonal antibodies that neutralize 1) a variety of cytokines (such as IL-1 alpha, IL-17 [36, 37], IL-12/23, IL-23), 2) cytokine receptors (such as IL-6 receptor) [38], or 3) adhesion molecules that are preferentially expressed in a specific organ like alpha 4 integrin. Bispecific antibodies that recognize more than one cytokine are currently under study [39]. Antagonists that neutralize vascular endothelial growth factor can be injected intravitreally to treat neovascularization or macular edema [40], especially in a patient whose intraocular pressure rises unacceptably after regionally injected corticosteroid. Soluble receptors such as etanercept, abatacept, or aflibercept can be used to block specific ligands or to interfere with cell to cell communication. Inhibitors of the JAK-STAT signaling cascade can be given orally and will inhibit multiple cytokines. JAK-STAT inhibitors are being used to treat rheumatoid arthritis [41], psoriatic arthritis [42], and inflammatory bowel disease [43]. The JAK-STAT inhibitor, filgotinib, is under study at the moment in a multi-center randomized controlled trial to treat uveitis. The efficacy of intravitreal corticosteroid delivery has encouraged other intravitreal approaches with the hope to identify medications that are effective without raising intraocular pressure or causing cataract. Intravitreally delivered sirolimus has demonstrated some efficacy in treatment of uveitis in a randomized trial [44]. The eye is a semi-closed chamber which makes it an attractive organ to treat inflammation via gene delivery. This has proven successful for inherited retinal disease [45] and has potential in the treatment of uveitis.

Many issues relating to uveitis require greater scrutiny. For example, we are only beginning to learn when immunosuppression can be stopped [46]. Biomarkers have the potential to help therapy become more targeted based on an individual's profile and prognosis. Idiopathic uveitis remains a frustrating term in part because subsets of uveitis presumably respond differentially to therapy. And patients are often focused on diet, exercise, and non-pharmacologic treatments about which we know all too little.

Managing patients with uveitis

In The Healing of America, T.R. Reid describes his experience seeking treatment for his shoulder derangement. He visited 10 countries including the US and Japan. Although the goal is always the same, excellent health with minimal risk from treatment, the approach varies widely. I cannot vouch for how care is delivered in Japan; nor can I pretend that I know what is done in every US uveitis clinic. I can, however, share some aspects of my personal approach.

Shared decision making is a goal in most physician-patient encounters. It recognizes that patient preferences need to be considered in outlining a treatment plan. All medical advice involves a risk-benefit analysis. What can be gained by the treatment? What is the potential harm? I express this with the cliché: "the punishment should fit the crime". Diseases are like a crime; they create victims who suffer. But all medications represent punishment; they have costs, risks, and inconvenience. If the crime is minor (let's say mild anterior uveitis), the punishment should be gentle (topical corticosteroids). But if the crime is major (vision threatening posterior uveitis), treating with potent immunosuppression is often justified.

Another way that I conceptualize shared decision making is to describe my role as being similar to a server in a restaurant. A patient has choices just as you do when selecting from a menu. Preferences vary and there is not always a right choice and a wrong choice. I find that if a patient takes an active role in creating the treatment plan, the patient is more understanding of outcomes such as adverse effects or incomplete therapeutic response.

Oral corticosteroids are arguably the most common medication which I prescribe; the use of oral corticosteroids is fraught with side effects. I usually liken the use of prednisone to using water to extinguish a fire. We start with a high dose until the flames appear to be completely out. But we don't know if the flames will remain out if we stop

the treatment, so we reduce the dosage slowly and observe closely if any fire resumes.

Collaborating

Uveitis is often best managed by a multidisciplinary approach. A rheumatologist, neurologist, cardiologist, pulmonologist, dermatologist, oncologist, or infectious disease expert are among the specialists whom I call upon to optimize care. Collaborating with another physician is challenging. In some instances, it is ambiguous as to who is ultimately responsible. Patients may receive conflicting advice. Many of my rheumatology colleagues express frustration since they are prescribing potentially harmful medication for a disease they cannot assess. Many of my ophthalmology colleagues find it difficult to identify a rheumatologist who is knowledgeable and available to co-manage patients with ocular inflammation. The paradigm which is ideal is a multi-disciplinary clinic in which the ophthalmologist and the rheumatologist discuss the treatment plan jointly with the patient. But many logistic issues like space, efficient use of time, and compensation create challenges for this paradigm. I am aware of very few multidisciplinary clinics like this in the US, but I think that this approach has the potential to optimize care.

Summary

Uveitis is a major cause of visual loss. Although there is overlap between the causes of uveitis in Japan and the US, there are also important differences. The therapeutic armamentarium also differs between the two countries. Recent therapeutic advances based on randomized controlled trials have changed the approach for some patients with uveitis. But much remains to be done, especially with regard to studies on specific forms of uveitis. As therapy improves for a variety of inflammatory diseases, many novel treatments become tested for their potential role in the treatment of uveitis as well. The complexity of care and the relationship between an eye disease and disease elsewhere in the body mean that input from more than one specialist is of benefit to the patient. This collaboration is challenging but, when successful gratifying.

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