THE BURDEN OF NONINFECTIOUS UVEITIS OF THE POSTERIOR SEGMENT: A REVIEW

New pharmacologic treatment options are urgently needed.

BY STEVEN YEH, MD, AND JESSICA G. SHANTHA, MD


Noninfectious uveitis (NIU) is a serious, sight-threatening intraocular inflammatory condition characterized by inflammation of the uvea (iris, ciliary body, and choroid). For physicians caring for patients with uveitis, inflammatory eye disease involving adjacent structures (eg, scleritis, retinitis) is also included in the definition of uveitis.[1,2] Inflammation in NIU is driven by a T cell–mediated autoimmune process and perpetuated by proinflammatory cytokines.[1] NIU of the posterior segment of the eye, which includes intermediate, posterior, and panuveitis, is more difficult to treat than anterior uveitis and requires more complex therapeutic modalities.[3]

The varying etiologies of NIU of the posterior segment, which may be either systemic in nature or limited to the eye, may demonstrate differential responses to immunosuppressive medications.[2] Systemic autoimmune diseases associated with NIU include Behçet disease, ankylosing spondylitis and other human leukocyte antigen-B27–associated disease syndromes, and multiple sclerosis. Some patients may have ocular autoimmune disease without systemic disease associations, including birdshot retinochoroidopathy, multifocal choroiditis, and other white dot syndromes. Table 1 lists the diseases and syndromes associated with NIU that have been identified by the Standardization of Uveitis Nomenclature (SUN) Working Group.[4]

Timely diagnosis and effective management of NIU of the posterior segment are imperative to avert potentially severe vision loss. Intraocular inflammation can induce complications (eg, cystoid macular edema, cataract, secondary glaucoma, vitreous opacities, retinal scars) that, in turn, can cause cumulative structural ocular damage that may require escalation of medical or surgical therapy and lead to increased visual morbidity if not addressed (Figure 1).[3,5] Due to the rarity of NIU of the posterior segment and the lack of burden-related research, the burden of disease is not well understood. This article reviews some of the many areas in which the burden of NIU of the posterior segment can manifest in order to provide greater understanding of its effects on patients and society.

EPIDEMIOLOGIC IMPACT

Uveitis of any cause is a rare disease, but it is associated with a high risk of vision loss. It has been estimated to be responsible for 5% to 20% of all cases of legal blindness in the United States and Europe and 25% of blindness in the developing world.[6] Moreover, the age distribution of uveitis worsens the impact of the disease relative to other

AT A GLANCE

- NIU of the posterior segment of the eye is more difficult to treat than anterior uveitis and requires more complex therapeutic modalities.
- Timely diagnosis and effective management of NIU of the posterior segment are necessary to avert potentially severe vision loss.
- Treatment of NIU of the posterior segment presents substantial challenges and may in itself impose burdens on patients, but promising novel therapies are in late-stage development.

TABLE 1. DISEASES AND SYNDROMES ASSOCIATED WITH NONINFECTIOUS UVEITIS*

- Acute posterior multifocal placoid pigment epitheliopathy
- Ampiginous choroiditis
- Behçet disease
- Birdshot choroiditis
- Intermediate uveitis, non–pars planitis type
- Intermediate uveitis, pars planitis type
- HLA-B27–associated acute anterior uveitis
- JIA-associated chronic anterior uveitis
- Multifocal choroiditis with panuveitis
- Multiple evanescent white dot syndrome
- MS-associated intermediate uveitis
- Punctate inner choroidopathy
- Serpiginous choroiditis
- Sympathetic ophthalmia
- Vogt-Koyanagi-Harada disease
- Tubulointerstitial nephritis and uveitis

*Adapted from the SUN Working Group[4]
Abbreviations: HLA, human leukocyte antigen; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis

sight-threatening conditions, with onset typically occurring in young or middle-aged patients. In a cohort study of 2619 uveitis patients treated at a single clinic in Austria, two-thirds of uveitis cases (any cause) were diagnosed between the ages of 17 and 60 years (Figure 2).[7] This distribution contrasts with more common sight-threatening diseases, such as diabetic retinopathy and age-related macular degeneration, which increase in incidence with age.[8]

NIU of the posterior segment comprises a substantial proportion of all cases of uveitis. In developed countries, the etiology of uveitis is noninfectious in approximately 80% to 90% of cases. Epidemiologic data on the anatomic location of the disease indicate that up to half of uveitis cases involve the posterior segment.[6] Accordingly, healthcare providers who treat uveitis can expect to encounter NIU of the posterior segment frequently in the clinic.

VISION LOSS

Uveitis exhibits an unpredictable and variable clinical course that may be sudden and limited in duration (acute), recurrent and interspersed with episodes of inactivity, or chronic and persistent.[2] It can be difficult to identify patients early in the disease course, given that onset may be insidious. There may be no symptoms before visual impairment,

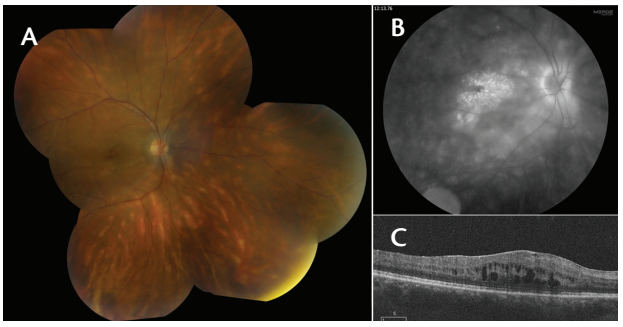

Figure 1. Fundus photo montage shows multiple oval, cream-colored lesions within the choroid in the right eye consistent with birdshot choroiditis (A). A venous phase fluorescein angiogram shows petalloid leakage and optic disc hyperfluorescence (B). Optical coherence tomography shows macular edema greater nasally leading to decreased visual acuity to 20/40 in the right eye (C).

especially in autoimmune conditions limited to the eye, and, consequently, patients may already have experienced vision loss at initial presentation.[1]

Loss of visual acuity in uveitis may be progressive if treatment is not initiated promptly, and rates of visual impairment or vision loss are high. In a study of 315 consecutive uveitis patients treated at a single uveitis referral service (mean age, 48 years; mean duration of follow-up, 36.7 months), 220 patients (70.0%) had visual impairment, defined as BCVA of 6/18 or worse in at least one eye. Within this group, 100 patients (45.4%) had moderate vision loss (6/18 to 6/36), and 120 (54.5%) had severe visual loss (6/60).

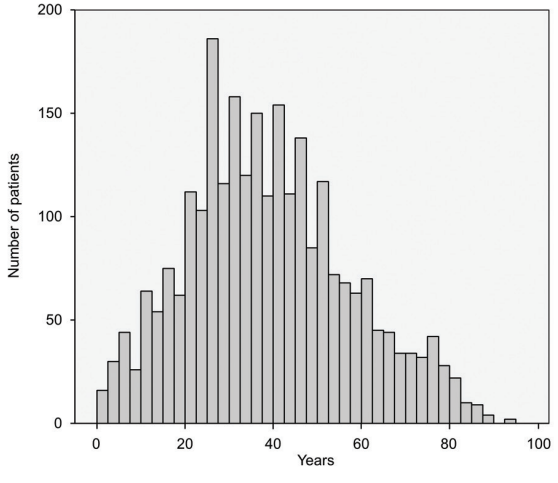

Figure 2. Age distribution of uveitis onset in a study of 2619 uveitis patients. *Reprinted with permission from Barisani-Asenbauer 2012.*[7]

TABLE 2. VISUAL IMPAIRMENT IN UVEITIS PATIENTS IN A UK TERTIARY CENTER[9]

Anatomic location of uveitis	Bilateral legal blindness n (%)	Bilateral visual impairment n (%)	Unilateral legal blindness n (%)	Unilateral visual impairment n (%)
Anterior uveitis (n = 246)	4 (2)	7 (3)	22 (9)	13 (5)
Posterior segment uveitis (n = 314)	18 (6)	27 (9)	57 (18)	49 (16)

Some degree of permanent ocular damage, such as macular scarring or atrophy, lamellar macular hole formation, optic atrophy, etc., was found in 54 of the 220 patients (24.5%) with vision loss; 11 had unilateral and 46 had bilateral ocular complications. Thirty-six of the 315 patients (11.4%) met World Health Organization criteria for blindness.[5]

Posterior uveitis is associated with worse visual outcomes compared with anterior uveitis. A study of 582 consecutive patients treated at two ophthalmologic referral centers compared rates of visual impairment in anterior and posterior uveitis.[9] As shown in Table 2, the prevalence of visual impairment and blindness was consistently greater with posterior than with anterior uveitis.

A study of 1799 eyes of 1076 patients with uveitis (any cause) treated at a single center found that eyes with posterior uveitis were significantly more likely than eyes with anterior uveitis to have permanent moderate visual loss (BCVA 20/50 to 20/120; 11.7% vs. 6.3%; $P < .001$), to have permanent severe visual loss (BCVA ≤ 20/200; 11.8% vs. 4.2%; $P < .001$), to require oral prednisolone (62.1% vs. 18.2%; $P < 0.001$), and to require high-dose (> 40 mg) oral prednisolone (40.3% vs. 6.5%; $P < .001$).[10]

VISUAL FUNCTION AND QUALITY OF LIFE

In many cases of posterior uveitis, currently available treatments are ineffective in halting the progression of vision loss. The severe limitations that visual deterioration imposes on patients in numerous areas, including employment, daily function, and quality of life, necessitate new therapies that can preserve visual acuity in NIU of the posterior segment.

A close relationship exists between visual function and vision-related quality of life in uveitis; performance on clinical tests of visual function directly correlates with scores on the Vision Specific Quality of Life Questionnaire.[11] Furthermore, perceptions of visual function are worse in those with NIU than in the general population. A study of 76 patients with NIU found that patient-reported scores on the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) were significantly worse than for a reference population, including overall score and all individual domains (eg, driving, social functioning, role limitation). Notably, posterior uveitis and panuveitis were associated with significantly worse scores than anterior NIU on the NEI VFQ-25 domains of general health, near vision, peripheral vision, and dependency.[12]

The effects of NIU extend beyond vision-specific quality of life. NIU patients perform worse than the general population on generic health-related quality-of-life measures, such as the mental and physical component scores and individual domains of the Medical Outcomes Study 36-Item Short Form (SF-36).[12,13] As would be expected, NIU patients with associated systemic disease have even worse scores on the SF-36 than those with NIU with only ocular manifestations.[12]

Health-related quality of life is severely impaired even in patients who are receiving immunosuppressive treatment and/or whose uveitis is well controlled. In the study mentioned above of 76 NIU patients with vision-related impairment on the NEI VFQ-25, 93% of the study group were receiving active treatment for their condition.[12] A clinic-based survey of 37 adolescents with quiescent uveitis and good visual function found that they had significantly lower health-related quality-of-life scores than their unaffected peers. In that population, the number of previous disease recurrences correlated with worse health-related quality of life on the Inventory for Assessing the Quality of Life in Children and Adolescents. Nearly two-thirds of respondents (62%) expressed fear about eventual blindness, indicating the detrimental effects of even quiescent disease on mental health and well-being.[14]

BURDEN OF TREATMENT

Treatment of NIU of the posterior segment presents substantial challenges and can be a burden for patients. Topical therapies are administered with relative ease, but they do not effectively penetrate the posterior segment and are thus considered a treatment adjunct for patients with NIU of the posterior segment, used primarily if there is also anterior segment inflammation. Medications targeting the posterior segment of the eye are difficult to deliver, their efficacy is not universal, and the available modalities all have associated risks. Additionally, the chronic nature of many cases of NIU may require treatment lasting over many years, which

contributes to the burden on patients.

Systemic corticosteroids are the standard of care for acute NIU, and these drugs can control inflammation in most patients. It is notable that in the recent MUST trial, nearly 30% of patients with NIU of the posterior segment receiving systemic corticosteroid therapy with standard-of-care corticosteroid-sparing immunosuppression continued to have active inflammation after 24 months of treatment.[15] The potential for debilitating adverse events with the prolonged use of systemic corticosteroids is well known, including increased risks for osteoporosis, hypertension, serious infections, pronounced weight gain, and mood disturbance, among other conditions.[16]

Guidelines for the chronic use of systemic corticosteroids in uveitis recommend maintenance dosages no higher than 10 mg/day to minimize the potential for serious adverse events,[17] but dosages used in real-world clinical practice are often much higher. A study of patterns in the treatment of NIU by specialists in the United States found that the mean oral corticosteroid dose throughout the chart review period was 38 mg/day to 46 mg/day, and the mean duration was 21 months.[18]

A recent survey quantified the perceived burdens of treatment from the perspective of 120 patients with NIU of the posterior segment. Common patient-reported adverse events among respondents taking systemic corticosteroids included weight gain or bloating (80%), trouble sleeping (70%), mood swings or irritability (60%), and increased appetite (55%). Half of patients taking noncorticosteroid immunosuppressants reported fatigue.[19]

Noncorticosteroid immunosuppressive agents have demonstrated modest efficacy in decreasing inflammation and reducing corticosteroid exposure,[20] but they have a narrow therapeutic index and also may have specific side effects that warrant monitoring. The SITE cohort study evaluated treatment outcomes in patients with ocular inflammation—including uveitis, scleritis, and ocular pemphigoid—who received such treatment. Control of inflammation with a prednisone dosage of 10 mg/day or less was maintained for 1 year by 55% of patients receiving mycophenolate, 36% receiving cyclosporine, 61% receiving cyclophosphamide, 58% receiving methotrexate, and 47% receiving azathioprine. During the same period, the percentages of those discontinuing due to adverse events was 12% for mycophenolate, 11% for cyclosporine, 34% for cyclophosphamide, 16% for methotrexate, and 24% for azathioprine. Specific safety concerns with these agents include bone marrow toxicity and liver enzyme elevation (mycophenolate, methotrexate, and azathioprine), renal disease (cyclosporine), and malignancy and hemorrhagic cystitis (cyclophosphamide).[21-25]

Intravitreal corticosteroid implants have demonstrated improvements in visual function and inflammation, but they are associated with increased risks for development of elevated intraocular pressure, glaucoma, and cataract.[26,27] Biologics (eg, infliximab [Remicade, Janssen Biotech], adalimumab [Humira, AbbVie]) have shown efficacy as corticosteroid-sparing agents, but these are the treatments least used by clinicians for this purpose because of concerns such as complexity of administration, safety and tolerability issues, and high cost.[28] Another concern is that tumor necrosis factor (TNF) inhibitors, specifically etanercept (Enbrel, Amgen), can paradoxically induce uveitis in some patients.[29,30]

The need for improved pharmacologic treatment is underscored by the fact that, even with pharmacotherapy, a substantial proportion of patients will require ocular surgery for uveitis-related complications. In a study of 1799 eyes in 1076 patients with any-cause uveitis (median follow-up, 5.6 years), 567 eyes (31.5%) underwent surgery, including cataract extraction, ocular filtration procedure to control elevated intraocular pressure, or vitrectomy.[10]

ECONOMIC BURDEN

The economic costs of NIU of the posterior segment have not been adequately explored, but available data suggest high direct and indirect disease-related costs. A database analysis calculated average direct medical costs in the year following uveitis diagnosis, based on information for 26 000 NIU patients in the United States. Average annual medical costs were higher for patients with NIU ($8450) than for controls with no uveitis ($4688), for patients with posterior segment NIU ($12 149) than for patients with anterior segment NIU ($7834), and for posterior segment NIU patients who were blind ($23 619) than those who were not ($11 607).[3] The MUST Trial Research Group conducted a cost-effectiveness study that compared the direct costs of systemic treatment (corticosteroids, immunosuppressant therapies) to those of corticosteroid implant therapy in NIU of the posterior segment. The costs of medication, surgeries, hospitalizations, and regular procedures (eg, laboratory monitoring for systemic therapy) were included. Cumulative costs of systemic therapy over 3 years were estimated to be $33 400 for a patient with unilateral disease and $52 500 for a patient with bilateral disease. The corresponding estimated costs for implant therapy were $38 800 for unilateral disease and $69 300 for bilateral disease.[26]

Regarding indirect costs, a survey of absenteeism in uveitis patients found that the need for sick time can be substantial, with employed respondents reporting sick leave due to ocular inflammation in the past year as high as 22 weeks (mean: 1.6 weeks).[32] A case-control study of privately insured US employees estimated annual mean indirect medical costs (including disability and medically related absenteeism) of $6902 for posterior segment NIU patients, which was significantly ($P < .05$) higher than for controls with no uveitis ($1612).[33]

Employment insecurity is less quantifiable, but this is

clearly an important concern for uveitis patients. In the survey of absenteeism, approximately 10% of patients with uveitis said they believed that they lost a job due to their illness, and the same proportion thought that they were at risk of losing their current job. These responses were especially noteworthy given that the surveyed population was receiving immunosuppressive therapy and that only six of the 46 respondents had some degree of visual field loss.[32]

As uveitis onset most commonly occurs during prime working years, the potential consequences for patients are considerable. Loss of income related to uveitis and its treatment remains to be quantified, whether in the uveitis population in general or in patients with NIU of the posterior segment in particular.

CONCLUSIONS

Although it is often considered a rare disorder, NIU of the posterior segment confers a significant impact on vision-related patient quality of life, both in issues related to visual impairment and in side effects associated with local and systemic immunosuppressive medications. The health impairment and the treatments associated with NIU of the posterior segment also carry economic burdens for patients and for healthcare systems, highlighting the fact that new pharmacologic options are urgently needed.

Novel therapies are in late-stage development for NIU of the posterior segment, and anticipated data on these agents will provide evidence on the validity of several potential new treatment strategies. Treatments in phase 3 clinical trials include an intravitreal formulation of sirolimus (Santen), which regulates T-cell function by inhibiting the mammalian target of rapamycin (mTOR); the biologics adalimumab (a TNF inhibitor) and gevokizumab (an anti–interleukin [IL]-1β antibody; Xoma/Servier), each of which is administered subcutaneously; and a new-generation, extended-release fluocinolone acetonide intravitreal implant (Retisert, Bausch + Lomb). Clinical trial data on these and other potential therapies will enhance understanding of the pathophysiology of NIU of the posterior segment, and one or more of these agents may in the future provide additional therapeutic options for patients. ■

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Steven Yeh, MD
- Louise M. Simpson Professor of ophthalmology, section of vitreoretinal surgery and diseases, and director, section of uveitis and vasculitis, Emory Eye Center, Atlanta, Ga.
- financial disclosure: consultant to Santen and Clearside Biomedical
- syeh3@emory.edu

Jessica G. Shantha, MD
- Emory Eye Center, Atlanta, Ga.
- financial interest: none
- jgshantha@gmail.com

Editorial support for the preparation of this article was provided by BioScience Communications, of New York, N.Y., funded by Santen.