S:T ERIKS ÖGON SJUKHUS

Ocular inflammation and infection course

Stockholm, 18–19 April 2024

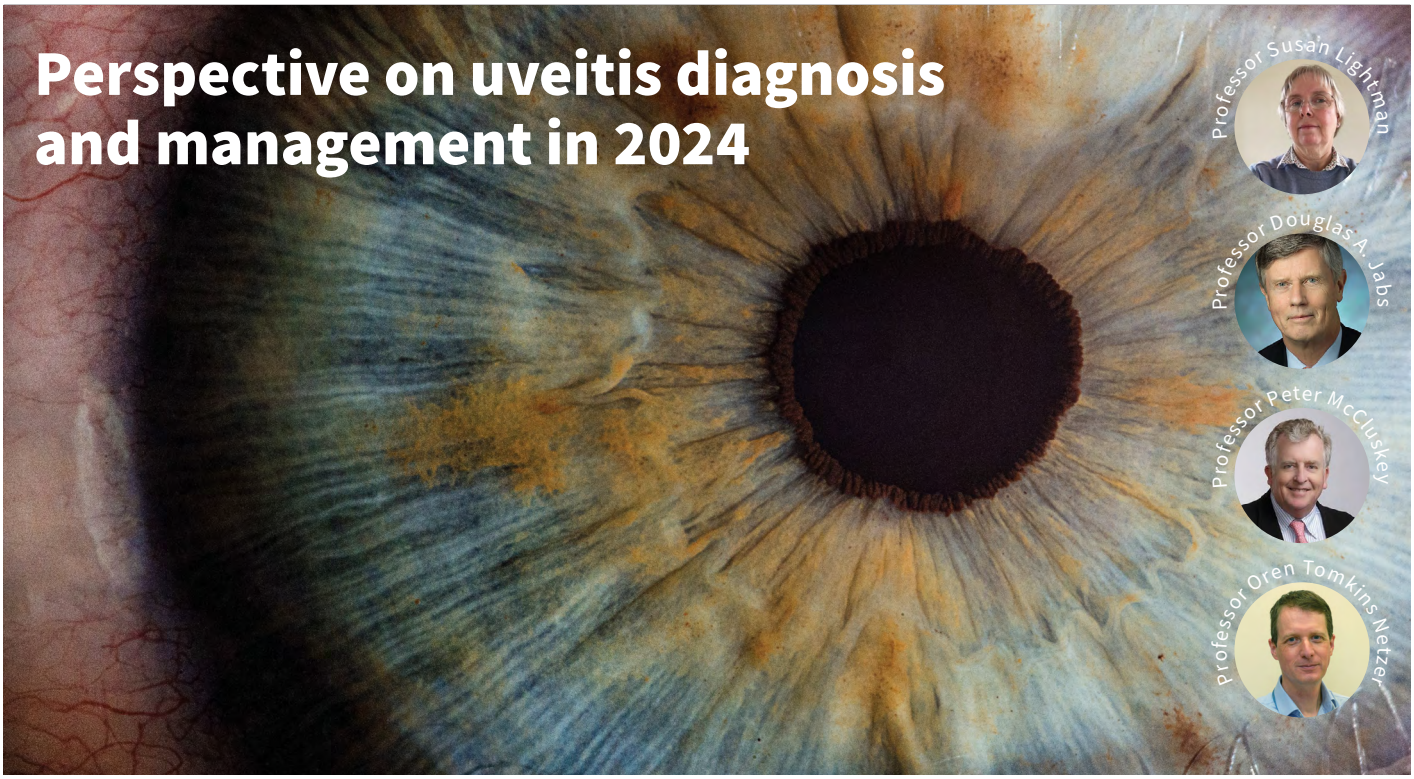

Photos: Eva Tov

Key take away messages

- Carefully examine the eye to define the location of the inflammation using SUN guidelines.
- Always consider infection.
- Selective use of laboratory investigations based on clinical findings.
- Control the inflammation and manage complications using evidence-based guidelines.

You can read more about uveitis diagnosis and management on page 15.

Perspective on uveitis diagnosis and management in 2024



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Introduction

The uveitides are a collection of over 30 diseases characterized by intraocular inflammation.[1] In resource-rich countries, they typically are the fifth-leading cause of blindness, and the cost of treating them is estimated to be similar to that of treating diabetic retinopathy.[2,3] In addition to the direct treatment-related costs of uveitis, the disease also has substantial indirect costs, as patients with uveitis require more annual visits for medical care, use more prescription medications, have more disability days, and have more medically related absenteeism and work loss days than individuals without uveitis.[4] Furthermore, because uveitis affects patients of all ages, it has a potentially higher impact on years of potential vision lost than age-related diseases. As such, it is critical to properly diagnose and manage patients with uveitis to minimize uveitis-related ocular complications and preserve vision.

*Table 1. Selected Uveitic Diseases**

Anatomic class†	Infectious‡	Systemic Disease Associated	Eye-limited
Anterior	Cytomegalovirus anterior uveitis	Juvenile idiopathic arthritis-associated anterior uveitis	Fuchs uveitis syndrome
	Herpes simplex virus anterior uveitis	Spondylarthritis/HLA-B27 associated anterior uveitis	Undifferentiated anterior uveitis
	Varicella zoster virus anterior uveitis	Tubulointerstitial nephritis with uveitis	
	Syphilitic anterior uveitis	Sarcoidosis-associated anterior uveitis	
	Tubercular anterior uveitis		
Intermediate		Multiple sclerosis-associated intermediate uveitis	Pars planitis
		Sarcoidosis-associated intermediate uveitis	Intermediate uveitis, non-pars planitis type (undifferentiated intermediate uveitis)
Posterior	Acute retinal necrosis	Sarcoidosis-associated posterior uveitis	Acute posterior multifocal placoid pigment epitheliopathy
	Cytomegalovirus retinitis		Birdshot chorioretinitis
	Syphilitic posterior uveitis		Multiple evanescent white dot syndrome
	Toxoplasmic retinitis		Multifocal choroiditis with panuveitis
	Tubercular posterior uveitis		Punctate inner choroiditis
			Serpiginous choroiditis
			Undifferentiated choroiditis
			Undifferentiated panuveitis with retinal vasculitis
Panuveitis	Syphilitic panuveitis	Behçet disease uveitis	Sympathetic ophthalmia
	Tubercular panuveitis		Undifferentiated panuveitis with choroiditis
		Sarcoidosis-associated panuveitis	Undifferentiated panuveitis with retinal vasculitis
		Vogt-Koyanagi–Harada disease (Early-stage and late-stage)	

**Adapted from Standardization of Uveitis Nomenclature (SUN) Working Group. Development of classification criteria for the uveitides. Am J Ophthalmol. 2021; 228:96-116. Used with permission. †Anatomic class determined by the primary site of ocular inflammation. ‡Infectious uveitides*

Diagnosis of the specific type of uveitis

The goal of diagnosing a patient with uveitis is to identify the specific uveitic disease. The older notion of the "etiologic diagnosis of uveitis" is problematic because of logical inconsistencies and a tendency to over-test using tests with low positive predictive values in an effort to determine the "cause" of the uveitis. Instead, ophthalmologists should diagnose the specific uveitic disease, much like rheumatologists diagnose rheumatoid arthritis or axial spondyloarthritis (ankylosing spondylitis) and not the "cause" of the arthritis. The diagnosis of a patient with uveitis is facilitated by a disciplined approach in which the uveitis is characterized in several dimensions, including its anatomic class, laterality, course, and morphologic features (**Table 1**). The anatomic class of the uveitis is based on the clinically identified primary site of inflammation (**Figure 1**) and is categorized as anterior, intermediate, posterior, or panuveitis.[1,5] Inflammation is primarily found in the anterior chamber in anterior uveitides; the vitreous in intermediate uveitides; the retina, retinal vasculature, and/or choroid in posterior uveitides; and all parts of the eye with no one site predominating in panuveitides.[1, 5] Some patients may have a combination of anterior and intermediate uveitis, which lacks chorioretinal involvement and should thus not be categorized as a panuveitis.[5] Imaging (e.g., optical coherence tomography, fluorescein angiography, and fundus autofluorescence) is used to assist in the diagnosis of posterior and panuveitides. Laboratory testing then is used parsimoniously to exclude diseases with a protean appearance that can present as any uveitic anatomic class (e.g., syphilis and sarcoidosis) and identify infections that require antimicrobial/antiviral treatment or systemic diseases that might affect health.[1] Uveitides that do not fit a specific uveitis diagnosis should be categorized as "undifferentiated" with the laterality, course, and anatomic class (e.g., undifferentiated bilateral chronic anterior uveitis).[5] The use of the term "idiopathic" for these diseases is discouraged because most non-infectious uveitides have unknown causes (i.e., idiopathic), and the use of this term leads to logical inconsistencies, such as calling chronic anterior uveitis in a child without a systemic disease idiopathic but referring to chronic anterior uveitis in a child with juvenile idiopathic arthritis as nonidiopathic.[1, 5]

Treatment approaches are based on the anatomic class of the uveitis and the specific uveitic disease.[6] Some uveitic diseases typically are monophasic, spontaneously remitting diseases with a good visual prognosis (e.g., multiple evanescent white dot syndrome [MEWDS] and acute posterior multifocal placoid pigment epitheliopathy [APMPPE]) that do not typically require treatment. A few uveitides are chronic diseases that do not require anti-inflammatory treatment (e.g., Fuchs uveitis syndrome). The initial treatment of anterior uveitides is typically topical corticosteroids, whereas that of intermediate, posterior, and panuveitides is oral corticosteroids, often with immunosuppression. The most common indication for immunosuppression is a uveitic disease known to require immunosuppression to adequately taper corticosteroids to safe levels.[6]

Despite the importance of the correct diagnosis of uveitides, arriving at a correct diagnosis can be difficult, and in the past, the agreement among uveitis experts on the specific uveitic diagnosis was moderate at best.[7] Therefore, a standard approach to classify the uveitides was needed. The Standardization of Uveitis Nomenclature (SUN) Working Group is an international group of approximately 100 experts in uveitis, ophthalmic imaging, informatics, and machine learning that came together to standardize the approach to uveitis classification, severity grading, and research outcomes.[5,8-9] The SUN "Developing Classification Criteria for the Uveitides" was an international, rigorous, multiphase project to develop classification criteria for 25 of the more common uveitides.[8,9] The phases of the project were: (1) informatics, (2) case collection, (3) case selection, (4) machine learning, and (5) consensus review and publication. The informatics phase developed a standardized language and ontogeny to describe the uveitides and created a standardized "drop-down menu" case collection form. The case collection phase involved the collection of a preliminary database of 5766 cases of the 25 uveitic diseases under consideration for the machine learning phase. Because of the absence of a gold standard for uveitic diagnoses and the known difficulties in agreement among uveitis experts,[7] case selection using formal consensus techniques was employed to develop a final database of 4046 cases that achieved a super-majority (>75%) agreement on the diagnosis. During the case selection phase, the consensus techniques employed permitted the super-majority agreement on including or excluding a case to be achieved in 99% of cases.[8] The machine learning phase employed several approaches to arrive at a Boolean set of criteria for each of the 25

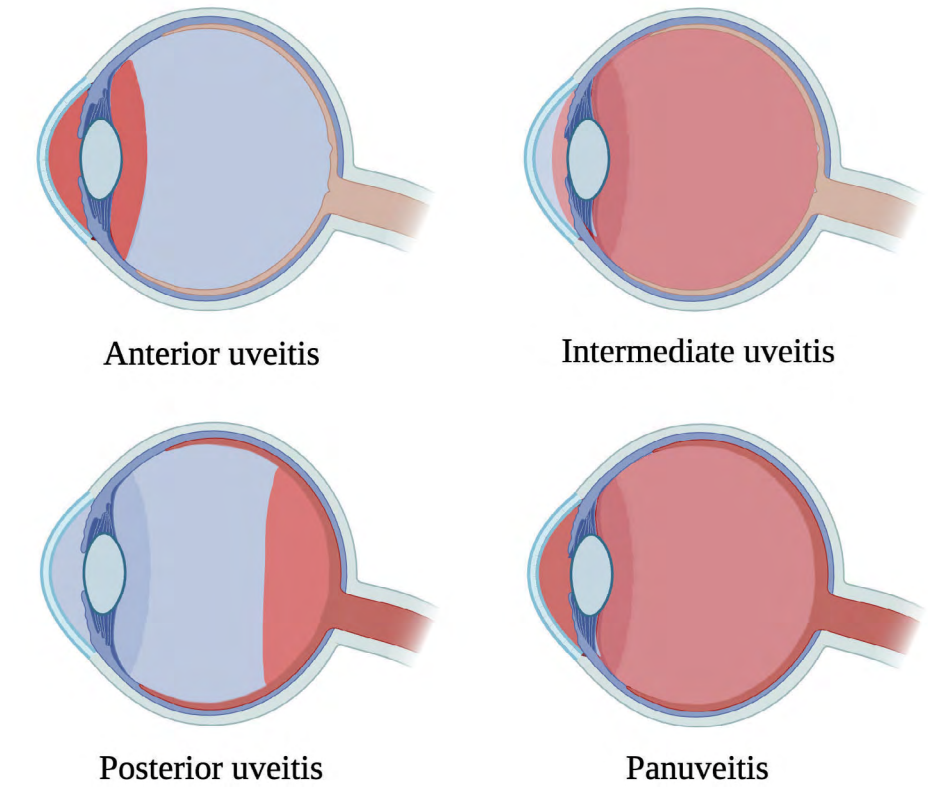

Figure 1. Diagnosis of specific uveitic disease and the Standardization of Uveitis Nomenclature (SUN) Classification Criteria - Anatomic classification of the uveitides. Areas colored red are where the inflammation/cells are located in the difference types of uveitis. Created with BioRender.com

diseases, and each approach produced similar results.[8] The accuracy of these diagnostic criteria was excellent, ranging from 93.3% to 99.3% depending on the anatomic class of the uveitis. The machine learning criteria were then translated into the final rules for each disease using the format developed for the International League Against Rheumatism (ILAR) criteria for juvenile idiopathic arthritis. The accuracy of the final rules was similarly excellent, ranging from 96.5% to 99.2% depending on the anatomic class.[8,9] The criteria were agreed upon at a meeting of the entire SUN Working Group and published as 26 articles (one with the methodology and 25 with the criteria for each disease) in a single issue of the *American Journal of Ophthalmology* in 2021.

Classification criteria are a form of diagnostic criteria used for research purposes.[10] Although they seek to optimize both sensitivity and specificity, when a trade-off is needed, they emphasize specificity to ensure a homogeneous group of patients for clinical and translational research purposes.[8,10] Nevertheless, the SUN classification criteria also appear to work well in clinical practice. An evaluation of the SUN classification criteria in clinical practice by an experienced clinician with familiarity with the SUN criteria revealed that agreement between the clinical diagnosis and the SUN classification criteria was achieved in 97% of cases,[9,11] suggesting clinical as well as research utility for the SUN classification criteria.

In conclusion, the proper diagnosis of the uveitides is necessary for proper long-term management and is facilitated by a standard, formalized approach.[1,5] The SUN classification criteria, although formulated for research use, also form an excellent basis for clinical diagnoses.[1,5]

Infectious uveitis

It is vital that infectious causes of uveitis are identified early, as they can cause irreversible damage in the eye very quickly, and treatment must be directed at the infecting agent. A broad range of infectious causes for uveitis account for up to 30% of cases in Caucasian populations. A wide spectrum of viruses, bacteria, fungi, and parasitic organisms can infect the eye in either immunocompetent or immunocompromised individuals. In our aging population, we increasingly recognize immunosenescence as a risk factor for infectious uveitis.[12]

Infectious uveitis can develop from exogenous spread—following trauma, surgery, or intravitreal therapy, by direct extension from corneal, scleral, or orbital infection—and endogenously from hematogenous spread. Organisms such as *Toxoplasma gondii* are neurotropic and preferentially infect the retina, while others, such as *Treponema pallidum*, infect any ocular structure. Herpes simplex and varicella-zoster viruses are also neurotropic and additionally become latent in neural ganglia. In many individuals infected with these viruses, relapses occur that often involve the eye, producing herpetic kerato-uveitis or herpetic retinitis (e.g., acute retinal necrosis [ARN] or herpes zoster ophthalmicus). Tuberculosis and syphilitic infections have long periods of latent infection, and their various ocular manifestations can mimic many other uveitic clinical phenotypes.

Many presentations of infectious uveitis are acute and associated with rapidly progressive vision loss. These patients face a serious threat to their vision and frequently present as emergencies, often after hours, on weekends, or during holiday periods when limited resources are available to assess and manage them. Such patients typically develop progressive vision loss in one or both eyes that increases over hours to several days. They may have symptoms of glare, photophobia, eye pain, redness, and increasing floaters. Clinical assessment is paramount and depends on a careful history and asking relevant medical questions about different body systems combined with a detailed examination of both eyes (**Table 2**).

Table 2. A thorough, detailed history

History
Systemic disease
All medications & drugs
Recent surgery, dental work, or illness
Ocular trauma
Travel history
At risk behavior - Intravenous drug use - At risk sexual activity
Immunocompromised - Immunosuppressive drugs - Immunosuppressive illness - Organ transplant - Cancer therapy - Past history of malignancy
+ Review of other parts of the body – gastrointestinal tract, genitourinary tract, respiratory tract, etc

It is often necessary to revisit the history after examining the eyes to ensure that all relevant details of the history have been gathered. The differential diagnosis for patients presenting with severe uveitis and vision loss is a critical one for all ophthalmologists. Importantly, most differential diagnoses are infective; these are detailed in **Table 3**.

Management of uveitis

After a clinician has decided on the type of uveitis present and ruled out an infective cause—often initially through clinical examination followed by investigations—they must manage the eye and any complications present. The objective of treating uveitis is to achieve a state of no inflammation and prevent the development of ocular complications that could result in irreversible vision loss.[13] For some diseases, treatment is needed only during acute episodes of active inflammation (e.g., HLA-B27-associated uveitis), whereas for chronic diseases (e.g. sarcoidosis, Behçet disease, or Vogt–Koyanagi–Harada syndrome), long-term treatment may be needed to control inflammation and prevent relapses.

Once a clinical diagnosis of uveitis is made, treatment is started immediately. Specific treatment choices are based on the potential causes, although immunosuppressive drugs are used in most cases of infectious and non-infectious uveitis. As the clinical findings become clearer and results from ancillary tests rule out certain causes, changes to treatment are made. For example, retinitis with dense vitritis may be caused by infectious diseases, such as viral retinitis or toxoplasmosis retinochoroiditis, or non-infectious diseases, such as Behçet disease. In such cases, initial treatment might include a combination of antibiotics, antivirals, and immunosuppressive drugs.

The cornerstone of treatment for non-infectious uveitides is corticosteroids, which can be delivered either locally or systemically. The choice of drug depends on its ability to penetrate the ocular barriers, its clinical efficacy, and its local or systemic side effects. Topical agents are typically most effective for anterior uveitis and ocular surface disease, although they differ in their ability to penetrate the cornea or sclera and their intraocular effect. Whereas methylated topical corticosteroids (e.g., prednisolone acetate and dexamethasone) cross the cornea easily—as do fluorinated agents, such as difluprednate—fluorometholone acetate has poor penetration and only a minimal intraocular effect.[14]

Intravitreal corticosteroids include triamcinolone acetonide injections, which are highly effective in controlling vitritis and treating uveitic macular edema.

Table 3. Differential diagnosis for severe uveitis & vision loss

Infectious	Acute retinal necrosis (herpetic retinitis)
	Endogenous endophthalmitis
	Exogenous endophthalmitis
	Toxoplasmic retinochoroiditis
	Syphilitic posterior or pan uveitis
	Tubercular posterior or pan uveitis
Immune mediated	Behçet posterior or pan uveitis
	Vogt Koyanagi Harada disease
Drug related	Drug induced posterior or pan uveitis

A dose of 4 mg is effective for up to 3 months. Corticosteroid implants are also very effective in treating non-anterior uveitis and macular edema[15-17] and last from 3 months (dexamethasone implant—Ozurdex®) to up to 30 months (fluocinolone inserts—Iluvien® and Yutiq®; implants—Retisert®).[15,18-20] Intravitreal corticosteroids have minimal systemic side effects but can result in elevated intraocular pressure (IOP) and cataract formation. The PeriOcular versus INTravitreal corticosteroids for uveitis macular edema (POINT) study[21] demonstrated a rapid resolution of macular edema for eyes treated with either intravitreal triamcinolone or a dexamethasone implant, although 40% required treatment for elevated IOP. The Macular Edema Ranibizumab versus Intravitreal Anti-inflammatory Therapy (MERIT) trial demonstrated that the dexamethasone implant was significantly better at treating persistent or recurrent macular edema than intravitreal methotrexate or ranibizumab.[22]

Systemic corticosteroids are used for vision-threatening chronic uveitis in bilateral disease when systemic disease requires treatment or the local corticosteroids are ineffective or contraindicated. Although highly effective, they have potential systemic side effects if used incorrectly at high doses for prolonged periods, and a tapering regimen is used to reduce their dose to a safe oral prednisone dose of <7.5 mg/day. The Multicenter Uveitis Steroid Treatment (MUST) study compared patients with non-anterior non-infectious uveitis treated with oral corticosteroids and systemic immunosuppression with those treated with a local fluocinolone implant (Retisert®).[18] At 24 months, both treatment arms were equivalent in the efficacy of controlling uveitis, the preservation of vision, and the profile of side effects. However, after 7 years follow-up, systemic treatment showed an advantage in the maintenance of vision.[23] In the MUST Trial, no increase in systemic side effects was observed with systemic therapy (versus the regional therapy with the fluocinolone acetonide implant) over 7–10 years of follow-up, except for greater use of antibiotics for infections in the systemic therapy group.[23]

Patients treated with systemic corticosteroids often need additional immunomodulatory agents to help reduce the dose of corticosteroids, and they may be started at the same time as the corticosteroids. They are used to help reduce the oral prednisone dose while maintaining inflammatory control. The Systemic Immunosuppressive Therapy for Eye disease (SITE) study demonstrated that a single-agent immunosuppression achieved uveitis control at 12 months in over 60% of eyes and successful corticosteroid-sparing in over 50% of patients.[24-26] The most common drugs are methotrexate and mycophenolate mofetil, although others, such as azathioprine, tacrolimus, and cyclosporine, are also options. The First-line Antimetabolites as Steroid-sparing Treatment (FAST) study compared the efficacy of methotrexate with that of mycophenolate mofetil among patients with non-infectious uveitis. The results revealed no significant difference in inflammatory control and successful corticosteroid-sparing between patients treated with methotrexate (66.7%) and those treated with mycophenolate mofetil (57.1%).[27]

Approximately 20–25% of patients treated with a single immunosuppressive agent require a second immunosuppressive agent to achieve successful corticosteroid-sparing (i.e., inactive uveitis and a prednisone dose of <7.5 mg/day).[28] Because most patients are treated with an antimetabolite (e.g., methotrexate or mycophenolate) as the first agent, the second agent is either a calcineurin inhibitor or a biologic agent. Although cyclosporine has been used extensively in the past, a randomized clinical trial demonstrated that tacrolimus was at least as effective as cyclosporine with less toxicity.[29] When used as the second agent in combination with an antimetabolite, tacrolimus treatment results in successful corticosteroid sparing in approximately 75% of patients by 6 months with adverse event rates similar to those of other immunosuppressive agents.[30]

More recently, biologic agents were shown to be effective in controlling inflammation in non-infectious uveitis. Anti-tumor necrosis factor α (TNFα) agents are most often used to treat non-infectious uveitis, and adalimumab received regulatory approval in the UK, US, and other countries. Patients treated with adalimumab in clinical trials had an approximately 50% reduction in relapse rate compared with those treated with placebo.[31,32] Adalimumab is approved as a treatment for intermediate, posterior, and panuveitis and is commonly used for patients with these types of uveitis. In Behçet disease, biologic agents should be used early,[33,34] and in children with juvenile idiopathic arthritis-associated uveitis, they should be used following failure with methotrexate.[35,36] No comparative data are currently available on the relative efficacy of anti-TNF agents (e.g., adalimumab) with conventional immunosuppressive agents. However, the ongoing Adalimumab Vs. Conventional Immunosuppression for Uveitis (ADVISE) Trial should help address this issue.[37]

Treating uveitis can be challenging, and clinicians must weigh the objective of preserving vision with the risk of side effects. The availability of many different drugs with various modes of administration and action provides us with the ability to tailor treatment options to each patient depending on the degree of inflammation, risk to vision, and drug tolerability. Systemic treatment is very effective in controlling uveitis and can be safe in the long term, although clinicians must continue careful monitoring, taper corticosteroids to a safe dose, and consider using immunosuppressive drugs and biologics as needed. Local treatment is typically used in cases of anterior uveitis and may be helpful in selected patients with non-infectious intermediate, posterior, or panuveitides who cannot tolerate systemic therapy and patients in whom tolerable systemic therapy is not effective in controlling inflammation.

Adjunctive regional therapy often is needed to treat macular edema, even when the uveitis is controlled by systemic

therapy. The POINT trial demonstrated that intravitreal corticosteroid injections were superior to periocular (e.g., posterior superior sub-Tenon's or retrobulbar/orbital floor injections) for treating uveitic macular edema and improving visual acuity.[21] In the POINT trial, intravitreal triamcinolone acetonide produced results similar to the intravitreal dexamethasone implant (Ozurdex®). Although crossovers to intravitreal therapy were allowed after the failure of periocular therapy, periocular therapy never caught up to initial intravitreal therapy in terms of visual improvement. The MERIT trial compared repeated intravitreal corticosteroids to intravitreal methotrexate or intravitreal anti-VEGF (ranibizumab) for persistent or recurrent macular edema, in a quiet eye, after an intravitreal corticosteroid injection.[22] Intravitreal corticosteroids (the dexamethasone implant) were superior to both intravitreal methotrexate and intravitreal ranibizumab for this indication, and only intravitreal corticosteroids produced an improvement in visual acuity.

Key points:

- The goal of diagnosing a patient with uveitis is to identify the specific uveitic disease characterized in several dimensions, including anatomic class, laterality, course, and morphologic features.
- Infective causes should always be considered.
- Treatment approaches are based on the anatomic class of the uveitis and the specific uveitic disease.
- The objective of treating uveitis is to achieve a state of no inflammation and prevent the development of ocular complications that could result in irreversible vision loss.

Future areas of research:

- The use of biologic agents as second-line instead of third-line agents, as they are currently used in many inflammatory eye diseases
- The best drug combinations to allow optimal disease control without the need for systemic steroids
- Steroid eye drops that are effective in controlling inflammation but do not raise eye pressure
- Topical medication that can reach the posterior segment of the eye to control inflammation and its complications without the need for systemic medication or intraocular injections

Conflict of interest:

- **SL**: an investigator in the SUN project
- **DAJ**: AbbVie donated adalimumab to the Coordinating Center for the NEI-funded ADVISE Trial
- **PM**: an investigator in the SUN project, member of SUN Executive Committee
- **OTN**: received honorarium (Roche) and was on a Data Safety Monitoring Board or Advisory Board (Bayer)

References

1. Jabs DA, Busingye J. Approach to the diagnosis of the uveitides. *Am J Ophthalmol* 2013;156(2):228-36.
2. Nussenblatt RB. The natural history of uveitis. *Int Ophthalmol* 1990;14(5-6):303-8.
3. de Smet MD, Taylor SR, Bodaghi B, et al. Understanding uveitis: the impact of research on visual outcomes. *Prog Retin Eye Res* 2011;30(6):452-70.
4. Thorne JE, Skup M, Tundia N, et al. Direct and indirect resource use, healthcare costs and work force absence in patients with non-infectious intermediate, posterior or panuveitis. *Acta Ophthalmol* 2016;94(5):e331-9.
5. Jabs DA, Nussenblatt RB, Rosenbaum JT, Group SoUNSW. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;140(3):509-16.
6. Jabs DA. Immunosuppression for the Uveitides. *Ophthalmol* 2018;125(2):193-202.
7. Jabs DA, Dick A, Doucette JT, et al. Interobserver Agreement Among Uveitis Experts on Uveitic Diagnoses: The Standardization of Uveitis Nomenclature Experience. *Am J Ophthalmol* 2018;186:19-24.
8. Group SoUNSW. Development of Classification Criteria for the Uveitides. *Am J Ophthalmol* 2021;228:96-105.
9. Jabs DA, McCluskey P, Palestine AG, et al. The standardisation of uveitis nomenclature (SUN) project. *Clin Exp Ophthalmol* 2022.
10. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria? *Arthritis Care Res (Hoboken)* 2015;67(7):891-7.
11. Mudie LI, Reddy AK, Patnaik JL, et al. Evaluation of the SUN Classification Criteria for Uveitides in an Academic Uveitis Practice. *Am J Ophthalmol* 2022;241:57-63.
12. Akinsoji E, Goldhardt R, Galor A. A Glimpse into Uveitis in the Aging Eye: Pathophysiology, Clinical Presentation and Treatment Considerations. *Drugs Aging* 2018;35(5):399-408.
13. Tomkins-Netzer O, Talat L, Bar A, et al. Long-term clinical outcome and causes of vision loss in patients with uveitis. *Ophthalmol* 2014;121(12):2387-92.
14. Amon M, Busin M. Loteprednol etabonate ophthalmic suspension 0.5 %: efficacy and safety for postoperative anti-inflammatory use. *Int Ophthalmol* 2012;32(5):507-17.
15. Lowder C, Belfort R, Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol* 2011;129(5):545-53.
16. Tomkins-Netzer O, Lightman S, Drye L, et al. Outcome of Treatment of Uveitic Macular Edema: The Multicenter Uveitis Steroid Treatment Trial 2-Year Results. *Ophthalmol* 2015;122(11):2351-9.
17. Tomkins-Netzer O, Lightman SL, Burke AE, et al. Seven-Year Outcomes of Uveitic Macular Edema: The Multicenter Uveitis Steroid Treatment Trial and Follow-up Study Results. *Ophthalmol* 2021;128(5):719-28.
18. Kempen JH, Altaweel MM, Holbrook JT, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. *Ophthalmol* 2011;118(10):1916-26.
19. Testi I, Pavesio C. Preliminary evaluation of YUTIQ™ (fluocinolone acetonide intravitreal implant 0.18 mg) in posterior uveitis. *Ther Deliv* 2019;10(10):621-5.
20. Jaffe GJ, Lin P, Keenan RT, et al. Injectable Fluocinolone Acetonide Long-Acting Implant for Noninfectious Intermediate Uveitis, Posterior Uveitis, and Panuveitis: Two-Year Results. *Ophthalmol* 2016;123(9):1940-8.
21. Thorne JE, Sugar EA, Holbrook JT, et al. Periocular Triamcinolone vs. Intravitreal Triamcinolone vs. Intravitreal Dexamethasone Implant for the Treatment of Uveitic Macular Edema: The PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) Trial. *Ophthalmol* 2019;126(2):283-95.
22. Acharya NR, Vitale AT, Sugar EA, et al. Intravitreal Therapy for Uveitic Macular Edema-Ranibizumab versus Methotrexate versus the Dexamethasone Implant: The MERIT Trial Results. *Ophthalmol* 2023;130(9):914-23.
23. Kempen JH, Altaweel MM, Holbrook JT, et al. Association Between Long-Lasting Intravitreous Fluocinolone Acetonide Implant vs Systemic Anti-inflammatory Therapy and Visual Acuity at 7 Years Among Patients With Intermediate, Posterior, or Panuveitis. *JAMA* 2017;317(19):1993-2005.
24. Gangaputra S, Newcomb CW, Liesegang TL, et al. Methotrexate for ocular inflammatory diseases. *Ophthalmol* 2009;116(11):2188-98.e1.
25. Daniel E, Thorne JE, Newcomb CW, et al. Mycophenolate mofetil for ocular inflammation. *Am J Ophthalmol* 2010;149(3):423-32.e1-2.
26. Kaçmaz RO, Kempen JH, Newcomb C, et al. Cyclosporine for ocular inflammatory diseases. *Ophthalmol* 2010;117(3):576-84.
27. Rathinam SR, Gonzales JA, Thundikandy R, et al. Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs Methotrexate on Inflammation in Patients With Uveitis: A Randomized Clinical Trial. *JAMA* 2019;322(10):936-45.
28. Goldberg NR, Lyu T, Moshier E, et al. Success with single-agent immunosuppression for multifocal choroidopathies. *Am J Ophthalmol* 2014;158(6):1310-7.
29. Murphy CC, Greiner K, Plskova J, et al. Cyclosporine vs tacrolimus therapy for posterior and intermediate uveitis. *Arch Ophthalmol* 2005;123(5):634-41.
30. Jabs DA, Thorne JE, Wilkins CS, et al. TACROLIMUS FOR IMMUNOSUPPRESSION IN PATIENTS WITH NONINFECTIOUS INTERMEDIATE, POSTERIOR, OR PANUVEITIDES. *Retina* 2023;43(9):1480-6.
31. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet* 2016;388(10050):1183-92.
32. Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med* 2016;375(10):932-43.
33. Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmol* 2014;121(3):785-96.e3.
34. Al-Janabi A, El Nokrashy A, Sharief L, et al. Long-Term Outcomes of Treatment with Biological Agents in Eyes with Refractory, Active, Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. *Ophthalmol* 2020;127(3):410-6.
35. Quartier P, Baptiste A, Despert V, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis* 2018;77(7):1003-11.
36. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. *N Engl J Med* 2017;376(17):1637-46.
37. Jabs DA, Berkenstock MK, Altaweel MM, et al. The Conundrum of Clinical Trials for the Uveitides: Appropriate Outcome Measures for One Treatment Used in Several Diseases. *Epidemiol Rev* 2022;44(1):2-16.