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Updates in Uveitis Diagnostic Measures and Treatment: A Review

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ABSTRACT

Uveitis diagnosis and management have come a long way in recent years. The advancements in imaging techniques, molecular diagnostic tools, serologic testing, and uveitis management has become more accurate and timelier. In this review we shed light on the recent updates in regard to uveitis diagnostic measures and treatment plans.

Keywords: Uveitis; Diagnostic measures; Serologic testing; Ocular Inflammation; Optical Coherence Tomography; Choroiditis; Fundus Autofluorescence (FAF); Uveitis classification

BACKGROUND

Uveitis is a complicated and potentially blinding condition caused by inflammation of the uvea, which includes the iris, ciliary body, and choroid.[1] Other ocular structure, such as the retina and vitreous, may also be affected.[1,2] Uveitis diagnosis and treatment have evolved over time, with new trends emerging to improve patient outcomes. In recent years, advances in multimodal imaging have significantly contributed to improving the diagnosis and management of uveitis.[3] In this short review, we will try to highlight some of the most recent advances in uveitis diagnostic and management measures.

METHODOLOGY

In this review, PubMed, Medline, Springerlink, the Cochrane Library, Google Scholar, and EMbase Medline database of the last 7 years have been searched to retrieve English articles with the following key terms: “Uveitis,” “Uveitis diagnostic imaging”, “Uveitis trials,” “Uveitis management”, “Gene therapy in Uveitis”, Also, we considered STROBE systematic review methodology while searching for various papers for a recent and updated papers in regard to diagnostics and management of uveitis.

Classification of Uveitis.[1],

1. Anatomical Classification of Uveitis

Type	Primary Site of Inflammation*	Includes
Anterior uveitis	Anterior chamber	Iritis
		Iridocyclitis
Intermediate uveitis	Vitreous	Pars planitis
Posterior uveitis	Retina or choroid	Focal, multifocal or
		diffuse choroiditis
		Chorioretinitis
		Retinochoroiditis
		Retinitis
		Neuroretinitis
Panuveitis	Anterior chamber, vitreous	
	and retina or choroid	

2. Uveitis Classification Based on Course: Uveitis is classified as acute or chronic, according to the Standardisation of Uveitis Nomenclature (SUN) Working Group proposal. Acute uveitis is an intraocular inflammation that occurs suddenly and lasts less than three months. Chronic uveitis, on the other hand, usually develops slowly and lasts for more than three months. The duration of untreated inflammation determines whether uveitis is acute or chronic. In natural clinical practise, this is undeniably not the case. The author, in fact, categorises it primarily based on its onset, clinical manifestations, previous attacks, and associated systemic diseases.[4]
3. Uveitis specialists must be well-versed in all entities, and their work-up must include systemic and ocular examinations. Furthermore, the unique problems of varying socioeconomic, demographic, and morbidity patterns in different parts of the world can affect differential diagnosis. Because of a lack of good primary health care, low affordability, and poor compliance, the prevalence and severity of diseases in economically disadvantaged populations differ from those in the rest of the world.[5]

Ophthalmologists are still struggling to diagnose intraocular inflammations. In some cases, it is difficult to make a precise etiological diagnosis. There have recently been several advances in the investigation of uveitis, which has greatly aided ophthalmologists in the management of such clinical conditions.[1,2,3]

Radiological studies can often help in the diagnosis of uveitis. Imaging is essential in the diagnosis of uveitis, particularly posterior uveitis. Since the early 1960s, when Novotny and Alvis invented fluorescein angiography (FA), there has been constant progress with the introduction of new modalities, beginning with indocyanine green angiography (ICGA) and the publication of its schematic interpretation in uveitis.[2] Non-invasive methods such as optical coherence tomography (OCT), blue light fundus autofluorescence (BAF), enhanced depth imaging OCT (EDI-OCT), and, finally, OCT-angiography (OCT-A) were used to investigate posterior uveitis.[1,2,3]

Imaging techniques are particularly important in severe diseases such as intraocular tuberculosis. They play an important role in determining the disease pattern, which is required for a presumptive diagnosis of tuberculosis-associated uveitis. This is especially significant because Mycobacterium tuberculosis microbiological evidence is almost never present in these patients.[6]

The most common radiological finding in systemic sarcoidosis is bilateral hilar lymphadenopathy (BHL), which is considered pathognomonic for this clinical entity. It is present in 50%-89% of sarcoidosis cases, and the presence of BHL determines the stage 1 of pulmonary sarcoidosis.[7,8]

UPDATE ON DIAGNOSIS OF UVEITIS

Accurate diagnosis is critical for effective uveitis management. Recent advances in uveitis diagnosis emphasize the use of advanced imaging and laboratory investigations to support the identification of the underlying etiology and the development of appropriate management strategies. This section discusses the advancements in this field.

Advanced Imaging Techniques:

1. Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA): OCT has proven to be an invaluable tool in the diagnosis and monitoring of uveitis. OCT enables high-resolution cross-sectional imaging of the retina, allowing clinicians to detect subtle changes in retinal architecture associated with uveitic conditions and identify a variety of specific entities.[1-3] In recent years, OCT has evolved from Spectral-Domain OCT (SD-OCT) to Swept Source OCT (SS-OCT).[4,5]

Anterior segment OCT can also provide detailed visualization of anterior chamber structures, which can help in the diagnosis of anterior uveitis. Agarwal and colleagues used OCT scans to visualize inflammatory cells in the anterior chamber as hyperreflective dots in a pilot study.[11] One of the benefits of this new modality is its ability to detect anterior chamber cells even in eyes with corneal haze or edema.[11]

OCT-based methods have also been used to objectively assess vitreous haze.[12] Furthermore, OCT is being used as an intraoperative surgical guidance tool, with the potential to influence decision making and outcomes in complex uveitis cases.[12,13] The Determination of Feasibility of Intraoperative Spectral Domain Microscope Combined/Integrated OCT Visualization during En Face Retinal and Ophthalmic Surgery (DISCOVER) study looked at the role of intraoperative OCT in ophthalmic surgery and concluded that intraoperative OCT is a valuable tool that can influence surgical decision making and outcomes.[13]

The next major advancement in iOCT systems was the integration of OCT and the microscope's optics, which allow real-time OCT-based visualization of instrument-tissue interaction and immediate imaging with surgeon feedback.[14] To improve the stability and quality of the captured images, Z-tracking and focus controls were added to the device.[14] Currently, three FDA-approved systems are available: the Haag-Streit ® iOCT, the Zeiss Rescan® 700, and the Leica EnFocus®, all of which use spectral-domain OCT technology. For improved functionality, newer systems incorporate swept-source technology and 3D heads-up display.[15,16] According to the study done by Falkner-Radler et al, iOCT-guided membrane peeling was possible without the use of surgical staining agents in 40% of cases. Intraoperative OCT can also be used to diagnose macular holes and assess vitreous schisis.[17]

More recent significant contributions have been obtained with OCT angiography (OCT-A) utilizing a non-invasive study of the vascularization of the iris, retina, and choroid, allowing for more accurate detection of ischemia and neovascularization. When compared to primary cases, intraoperative OCT provided valuable insight in complex re-detachment (ie: repair) cases (50% vs 22%, with a statically significant difference (P value =0.01).[18] According to a review of the DISCOVER study, surgeons considered iOCT valuable in 50.6% of cases

underwent proliferative diabetic retinopathy surgery and it influenced the surgical decision-making in 26% of cases.[19]

Intraoperative OCT can confirm the integrity of scleral wound closure during Retisert fluocinolone acetonide implant placement (Bausch & Lomb®) in 84.6% of cases in uveitis-related vitreoretinal surgery.[19] Furthermore, it was found helpful in 81.2% of chorioretinal biopsies by guiding biopsy site selection and determining whether there is enough subretinal material to perform a successful biopsy.[20] Although intraoperative OCT has shown promise in improving surgical outcomes, it has limitations, including the light-scattering and shadowing effects of metallic instruments, which are affected by the patient, the eye, or the instrument motion, resulting in motion artefacts and distortions.[21,22]

Swept-source (SS) OCTA combines the benefits of more than 100,000 A-scans in a short acquisition time with improved depth resolution and dyeless angiography to provide critical anatomical alterations in ocular inflammation. In the context of uveitis, OCTA can help diagnose conditions affecting the choriocapillaris/retinal pigment epithelium (RPE), such as white dot syndromes, choroidal stromal pathologies like Vogt-Koyanagi-Harada (VKH) syndrome, and infectious diseases like ocular toxoplasmosis.[23]

OCTA is very useful in determining the area of choriocapillaris flow deficit corresponding to active choroiditis lesions in autoimmune Serpiginous choroiditis (SC), tubercular serpiginous-like choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), and multifocal choroiditis (MFC),[24] OCTA is also useful in detecting type 1 and type 2 choroidal neovascularization (CNV) in cases with choroiditis.[25]

OCTA distinguishes VKH from central serous chorioretinopathy (CSC) in atypical cases by displaying hypo-reflective 'dark dots' in the choriocapillaris layer in VKH that are absent in CSC eyes. the OCTA can also be used to determine the level of inflammation and the need for ongoing immunosuppression in VKH based on the appearance/disappearance of hypo-reflective ‘dark dots’.[25] In ocular toxoplasmosis, OCTA is very sensitive in detecting CNV.[26] The OCTA can be used to assess the retinal vasculitis.[26] Microvascular changes, including the area of the foveal avascular zone, can be easily assessed and quantified in Behcet's disease.[27,28]

Non-perfusion areas in conditions with occlusive retinal vasculitis can be delineated using OCTA and it might be, the OCTA superior to fluorescein angiography in detecting ischemic changes.[23,29]

OCT with increased depth: The addition of Enhanced Depth Imaging (EDI) to most OCT devices allowed in-depth histologic examination of the choroid. Several studies have been conducted to investigate choroidal thickness using this EDI mode of SD-OCT in patients with Behçet's Disease (BD).[9] Thus, OCT and OCTA as a multimodal imaging diagnostic tool adds value in uveitis cases.[14]

2. Ultrawide field imaging: Ultrawide field imaging refers to imaging modalities that can capture portions of the retina anterior to the vortex veins ampullae in a single frame, centered on the fovea.[23] Fundus color images, Fundus Autofluorescence (FAF), fluorescein angiography, and Indocyanine Green Angiography (ICGA) can all benefit from this technology. It provides simultaneous information of both the macula and the retinal periphery in uveitis, especially when used in conjunction with fluorescein angiography. It can detect retinal hypoperfusion and guide laser photocoagulation.[30] It is also used to monitor the degree of vitreous haze in cases of uveitis.

Poor pupillary dilatation due to posterior synechiae or inflammation is another challenge seen in uveitis patients. The ability to obtain images of the retinal periphery with ultrawide field imaging provides a significant benefit to the examiner.[23] The Ultrawide field imaging can also help with assessing and grading the sunset glow fundus that complicates VKH.[31,32] Thus, Ultrawide field imaging is especially important in uveitis, where repeated

examinations to monitor treatment response are frequently required and should include retinal periphery evaluation.

3. Fundus Autofluorescence (FAF): FAF is becoming increasingly popular for assessing the retinal inflammation and detecting subtle changes in the retinal pigment epithelium. It provides information about the cellular functional status of lipofuscin distribution in the retina. Performed usually with a confocal scanning laser ophthalmoscope (cSLO) that excites with 488 nm blue light, but other systems with different excitation light and barrier filters have been developed.[33] FAF can reveal white dot syndrome lesions such as multifocal choroiditis, punctate inner choroidopathy (PIC), and birdshot chorioretinopathy.[34]

However, in VKH, two patterns on FAF were observed in the acute phase and, interestingly, depending on the timing of therapy. Patients who received early intensive immunosuppression had mild hyper autofluorescence that decreased to normal in disease remission.[23] On the other hand, Patients who were not treated or who received a delayed treatment had diffused zones of hyper autofluorescence that resolved within 6 months into patchy hypo- and hyper autofluorescence areas.[35] As prompt treatment of VKH found to prevent permanent damage of the choroid.[23] The FAF demonstrates the required information about control of the disease.[35]

Fundus Autofluorescence (FAF) may also provide the photographic details helping in the monitoring of serpiginous choroiditis and ocular syphilis.[23,36] A new confocal microscopy (450 nm) blue-light FAF device has been introduced, which excites a different range of fluorophores, but its potential role in uveitis is still unknown.[36] Our understanding of pathologic changes in various vitreoretinal disorders has improved after the latest advances in fundus imaging technologies, as the use of ultra-widefield (UWF) imaging in the evaluation of the far periphery of the posterior segment.[37,38]

UWF FFA imaging also appeared to be clinically helpful for assessing the prognosis of Fuchs' uveitis syndrome (FUS) patients.[39]

4. Molecular Diagnostic Tools: Polymerase chain reaction (PCR) has been introduced couple of years ago in the methodology of diagnosing infectious uveitis by allowing the detection of microbial DNA or RNA directly from ocular samples. PCR-based assays have increased the accuracy and speed with which viral, bacterial, fungal, and parasitic infections associated with uveitis can be diagnosed. The ocular sampling of subjects is performed in the case of infectious uveitis.[40] Furthermore, multiplex PCR panels have been developed to test for multiple pathogens at the same time, improving diagnostic efficiency.[40]

A PCR test determines whether the genome of an infectious antigen, such as a virus, is active in the body. Using a PCR reagent, it amplifies and detects the target virus's gene.[40]

PCR has become a useful adjunct to the existing diagnostic procedure in the field of modern ophthalmology due to its simplicity, rapidity, sensitivity, and specificity. With the development of newer techniques such as multiplexing and real-time quantification, PCR has evolved into a powerful tool in molecular technology for analyzing very small amounts of DNA and RNA.[41]

Although the PCR test is used for all types of uveitis, it is most useful in posterior and panuveitis. This issue can be explained by the higher prevalence of infectious aetiologias in these entities, as well as the greater difficulty in performing reliable fundus examination.[42,43] A change in treatment plan may also result from PCR analysis of intraocular fluids. After PCR analysis, the therapeutic regimen was changed in 37% of patients in a study that included all classes of uveitis; this value was 20% in patients with posterior uveitis and 24% in cases with anterior uveitis.[42,43]

In a cohort prospective study of 86 Indonesian population with active uveitis, the RT-PCR were preformed looking for Mycobacterium tuberculosis, Toxoplasmosis gondii, cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, and rubella virus. The study compared the serology testing, RT-PCR, initial and final diagnosis. The aqueous RT_PCR diagnostic positivity rate found to be 20% while the rate of the infectious diagnosis was higher after RT_PCR (52%) compared to clinical presentation alone (44%). The study concluded that RT-PCR analysis of aqueous fluid in uveitis patients helped confirming one-third of cases.[44,45]

5. Serologic Testing: Serologic testing is critical in determining systemic associations with uveitis. Recent advances in detecting specific antibodies associated with various autoimmune diseases include the use of enzyme-linked immunosorbent assays (ELISA) and multiplex-based assays.[46] These tests aid in the diagnosis of diseases like sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada syndrome, and others. High yield of preliminary diagnosis based on systemic/ocular history and the clinical acumen of the ophthalmologist can lead to a diagnosis in 70% in uveitic conditions. In the remaining cases, a tailored laboratorial approach is required for identification (Table 1). These tests are eventually required to confirm the diagnosis and start the patient on the treatment, which may be diametrically opposed.[46]

Table 1: Immunological tests in uveitis

Immunological tests in uveitis		
Uveitic entity	Disease type	Immunological tests
Infectious Uveitis		
Bacterial disease	Tuberculosis	Mantoux Test, Interferon-gamma release Assay (IGRA) QuantiFeron-Gold In-Tube & T-SPOT TB
	Leprosy	Lepromin test
	Syphilis	Treponemal tests
		Non Treponemal tests
	Leptospirosis	Microagglutination test, ELISA
	Lyme disease	ELISA
	Rickettsia	ELISA Weil Felix test,
Viral diseases		
	HIV	ELISA. Westren Blot
	Dengue	ELISA, Plaque Reduction Neutralization test (PRNT)
	Chikungunya	ELISA, (PRNT)
	West Nile virus	ELISA, RT -PCR
Parasitic diseases		
	Toxoplasmosis	ELISA
	Toxocariasis	ELISA
Non-infectious Uveitis		
Collagen vascular disease	-Rheumatological disorders -Juvenile idiopathic arthritis - Systemic lupus erythematosus	Antinuclear Antibody dsDNA, ssDNA (double & single-stranded deoxyribonucleic acid,)
	Scleroderma	Anticentromere antibody,Sm
	Rheumatoid arthritis	Rheumatoid Factor: Anti-Cyclic Citrullinated Peptide

	Wegener's granulomatosis	Antineutrophil Cytoplasmic Antibody: C ANCA
	Polyarteritis nodosa (PAN) group	Antineutrophil Cytoplasmic Antibody: C ANCA, P ANCA

N.B.: T-SPOT.TB = Tuberculosis-specific enzyme-linked immunospot assay, ELISA = Enzyme Linked Immunosorbent Assay, PRNT = Plaque Reduction Neutralization Tests , RT-PCT=Reverse transcription polymerase chain reaction

Electrophysiological tests are useful in assessing many types of uveitis, particularly posterior uveitis. The electrophysiological examination is a type of objective ocular examination that includes electroretinograms, visual evoked potentials, electrooculograms, multifocal electroretinograms, and multifocal visual evoked potentials. Electrophysiological tests are typically used to supplement the ophthalmologic examination rather than as a diagnostic tool. ERG is the most commonly performed test in uveitic patients, and it is primarily used in the detection and localization of early retinal lesions, the monitoring of disease activity and progression, and the efficacy of treatment, particularly in the era of intravitreal therapies.[47,48]

UPDATE IN MANAGEMENT OF UVEITIS

Uveitis is a potentially blinding disease. It can be caused by an infection or by an autoimmune disorder. In cases of infectious uveitis, specific antimicrobial therapies with or without corticosteroids are used. Corticosteroids, immunosuppressive agents, and, more recently, biologics are among the medications available to treat noninfectious uveitis. With newer drugs and innovative advances in ocular drug delivery, the treatment of uveitis is evolving. This is due to a better understanding of disease pathophysiology and drug delivery barriers.[49]

The goal of uveitis treatment is to reduce inflammation, preserve vision, and avoid complications. Individualized treatment plans, targeted therapies, and the use of biologic agents are recent trends in uveitis management.[50] The goal of Non-Infectious Uveitis (NIU) therapy is to reduce inflammation and achieve complete remission, thereby reducing or eliminating ocular complications, permanent cumulative damage, and long-term vision loss.[50,51]

1. Individualized Treatment Plans: Uveitis has its complexity as a scope of diseases that share somehow similarity in clinical picture with numerous aetiologias and clinical manifestations. Recent developments highlighted the importance of tailoring plan of treatment to the specific subtype of uveitis and the underlying cause.[52] This method takes into consideration including the patient-specific factors, disease severity, anatomical location of inflammation and the associated systemic conditions. Individualizing treatment plan may include corticosteroids, immunosuppressive agents, or biologic therapies.[53]

2. Antimetabolites: Methotrexate (MTX), a folic acid analogue, is frequently used in both adults and children due to its well-studied safety and efficacy profile.[52] Its dose typically between 10-25 mg weekly. The MTX always paired with folic acid on a daily basis to help mitigate some of the medication's side effects, which include oral ulcers, gastrointestinal discomfort, and hair loss. Interstitial pneumonitis, changes in liver function tests, and bone marrow suppression are all serious clinical and laboratory manifestations.[54] For all patients on disease

modulating, chemotherapy or immunosuppressants the treating physician must have base-line lab test and follow the established guidelines for medication side effects mentoring via history taking, clinical exam and lab testing. Azathioprine and mycophenolate mofetil are two other antimetabolites that inhibit purine synthesis, preventing lymphocyte maturation.[55] In adult, the usual dose of Azathioprine is 1-3 mg/kg/day, while mycophenolate is given at a maximum of 1,500 mg twice a day. The most common side effects are gastrointestinal distress, but serious complications, such as bone marrow suppression, can occur.[56] As with methotrexate, baseline labs and lab work every three months should be performed to monitor for these. Only azathioprine is considered safe during pregnancy. Anti-metabolites should not be combined with another anti-metabolite in general, but they can be combined with other types of steroid sparing drugs, such as anti-TNF-medications.[57]

Table 2: Immunomodulatory therapies for the treatment on NIU.[55,56,57]

Class	Name
Antimetabolites	Azathioprine
	Methotrexate
	Mycophenolate Mofetil
Calcineurin Inhibitors	Cyclosporine
	Tacrolimus
Alkylating Agents	Chlorambucil
	Cyclophosphamide

3. Targeted Therapies: The development of targeted therapies has transformed the treatment of uveitis, which aims to inhibit specific molecules or pathways involved in the inflammatory process.[58]

In the majority of patients, periocular depot corticosteroid injections were effective in treating active intraocular inflammation and improving reduced visual acuity caused by macular edoema. The response pattern was consistent across anatomic uveitis locations.[59,60] The US Food and Drug Administration (FDA) approved the fluocinolone acetonide intravitreal implant 0.59 mg (Retisert, Bausch + Lomb) in 2005. It is surgically implanted to treat noninfectious intermediate uveitis, posterior uveitis, or panuveitis and has a three-year drug release period.[49,61] Preclinical studies revealed that the implant is well tolerated, with no evidence of systemic drug absorption.

In the United States and Europe, the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) is a sustained-release, injectable, biodegradable steroid implant approved for the treatment of noninfectious uveitis affecting the posterior segment.[6,7] Dexamethasone is released biphasically over a 6-month period by the device, which is implanted with a 22-gauge injector. The steroid concentration decreases after the first two months until month four, when it remains low until month six.[62,63]

Drugs for the treatment of uveitis, available and in the pipeline.[64]

Therapeutic Agent	Drug Class	Delivery Mechanism	Pivotal Clinical Trial (phase)
Structured fluocinolone implant (Retisert, Bausch + Lomb(	Corticosteroid	Sustained-release implant	FDA approved 2005. Re-implantation of a fluocinolone acetonide implant for non-infectious uveitis affecting the posterior segment (phase 4)

Injectable fluocinolone implant (Iluvien, Alimera Sciences)	Corticosteroid	Sustained-release implant	A Controlled, Multi-center Study of the Utilization and Safety of the MK II Inserter and the Safety of the FAI Insert in Subjects With Noninfectious Uveitis Affecting the Posterior Segment of the Eye (phase 3)
Dexamethasone implant (Ozurdex, Allergan)	Corticosteroid	Sustained-release implant	Study of the Effectiveness of Ozurdex for the Control of Uveitis (phase 4)
Suprachoroidal space TA (CLS-TA, Clearside Biomedical)	Corticosteroid	Suprachoroidal space	Suprachoroidal Injection of CLS-TA in Subjects With Non-infectious Uveitis (AZALEA) (phase 3) Suprachoroidal Injection of CLS-TA in Subjects With Macular Edema Associated With Noninfectious Uveitis (PEACHTREE) (phase 3)
Sirolimus (Opsiria, Santen)	mTOR inhibitor	Intravitreal	Intravitreal Sirolimus as Therapeutic Approach to Uveitis (SAVE-2)(phase 2) Study Assessing Double-masked Uveitis Treatment (SAKURA) (phase 3) A Phase 3b, Multinational, Multicenter, Open-Label Extension Study Assessing the Long-Term Safety of PRN Intravitreal Injections of DE-109 in Subjects With Non-Infectious Uveitis of the Posterior Segment of the Eye Who Have Participated in the SAKURA Development Program (32-009)
Adalimumab (Humira, Abbvie)	Anti-TNF-alpha	Subcutaneous	Efficacy and Safety of Adalimumab in Patients With Active Uveitis (VISUAL l) (phase 3) Intravitreal Adalimumab Versus Subcutaneous Adalimumab in Noninfectious Uveitis (IVAS) (phase 2) A Study of the Long-term Safety and Efficacy of Adalimumab in Subjects With Intermediate-, Posterior-, or Pan-uveitis (VISUAL III) (phase 3)
Tocilizumab (Actemra, Genentech)	Anti–IL-6	Intravenous	Study of the Safety, Tolerability, and Bioactivity of Tocilizumab On Patients With Non-infectious UVEITIS: The STOP-Uveitis Study (STOP-Uveitis) (phase 1/2)
Sarilumab (Kevzara, Sanofi Genzyme)	Anti–IL-6	Subcutaneous	SATURN study (phase 2)
YS606 (Eyevensys)	Anti–TNF-alpha	Electrotransfection injection system	Phase 1b study
EGP-437 (iontophoretic dexamethasone phosphate, Eyegate Pharmaceuticals)	Corticosteroid	Iontophoresis	Safety and Efficacy of Iontophoretic Dexamethasone Phosphate Ophthalmic Solution in Non-Infectious Anterior Uveitis (EGP-437-006)(phase 3)
NS ()Aldeyra Therapeutics)	Aldehyde trap	Topical	A Safety and Efficacy Study of NS2 in Patients With Anterior Uveitis (phase 2)
Corticotropin	Adrenocorticotropic hormone analogue	Subcutaneous or intramuscular	Phase 4 study

(Acthar, Mallinckrodt Pharmaceuticals)			

TNF antagonist topical ocular treatment could potentially avoid systemic exposure and its associated risks. However, the majority of TNF antagonists currently available (infliximab, adalimumab, and golimumab) are whole monoclonal antibodies. Most marketed TNF-alpha antagonists would not be expected to penetrate ocular tissues following topical application due to their biophysical properties, particularly their high molecular weights of approximately 150 kDa (whole IgG molecules).[65,66]

TNF-alpha (TNF-) inhibitors such as adalimumab and infliximab, for example, have shown efficacy in treating non-infectious uveitis. Interleukin-6 (IL-6) inhibitors, Janus kinase (JAK) inhibitors, and complement inhibitors are among the other targeted therapies being studied.[66] The TNF inhibitors approved by the FDA are infliximab, adalimumab, etanercept, golimumab, and certrolizumab.[58]

Licaminlimab was discovered to be the first biologic treatment demonstrated to have a treatment effect on an intraocular condition with topical ocular application in a recent randomised Phase II Pilot Study. The primary goal of the trial was met, and the observed responder rate for licaminlimab was 56.0%.[67]

4. Immunomodulatory Therapy (IMT): A key goal in the treatment of uveitis is to reduce the use of corticosteroids and their numerous ocular and systemic side effects.[68] Immunomodulatory therapy is an important treatment strategy in the treatment of noninfectious uveitis (NIU). The International Consensus Group for Fundamentals of Care for Uveitis (FOCUS) of uveitis specialists (both ophthalmologists and rheumatologists) outlined the following indications for non-corticosteroid systemic immunomodulatory therapy (NCSIT).[68]

A- Acute sight-threatening disease, chronic persistent inflammation, exudative retinal detachment, posterior and macular involvement, and binocular sight-threatening disease - are all examples of ocular factors. B-Failure of regional or systemic steroid therapy, high dosage of systemic steroid therapy, relapse after reduction of systemic steroid therapy, and steroid intolerance or need for steroid-sparing effect -are examples of therapeutic needs.[68,69]

5. Biologic Agents: Those are drugs made from complex molecules manufactured using living microorganisms, plants or animal cells. Many are produces using recombinant DNA technology. They are also referred sometimes as biopharmaceuticals or biological drugs. They have emerged as a promising treatment option for patients with refractory uveitis. These agents are intended to target specific immune system components involved in the pathogenesis of uveitis. TNF-inhibitors, IL-1 inhibitors (e.g., anakinra), and IL-6 inhibitors (e.g., tocilizumab) are common biologics used in the treatment of uveitis. The use of biologic agents necessitates careful patient selection, close collaboration between ophthalmologists and rheumatologists, and close monitoring for potential side effects. Anti-tumor necrosis factor (TNF) agents are CS-sparing therapies that can be used in addition to immunomodulators to treat patients with NIU.[69]

Adalimumab (AbbVie Inc., North Chicago, IL, USA), a human monoclonal antibody that inhibits TNF-a signaling, has been approved to treat noninfectious intermediate, posterior, and panuveitis.[70] Adalimumab's efficacy and safety have been studied in randomized, controlled clinical trials.[71] Eurelings et al. conducted a retrospective clinical cohort study to assess the efficacy, reasons for discontinuation, and side effect profiles of adalimumab in a real-world setting. Adalimumab-treated 341 patients (633 eyes) with noninfectious uveitis were included in the study. The recurrence-free survival interval for uveitis was 3.4 years with range of 0-13 years. 178 patients achieved inactive disease while taking adalimumab while 51 patients-maintained remission after

stopping the drug. Adalimumab had a tolerable side effect profile and was discontinued due to a lack of response, relapse, or reasons unrelated to treatment efficacy. Adalimumab levels were lower in patients with antibodies, and antibodies were found more frequently in patients receiving adalimumab monotherapy (P.01). Adalimumab was found to be effective for noninfectious uveitis patients while also having a manageable side effect profile. Despite the possibility of relapses, the majority of patients achieved inactive disease or remission after discontinuing adalimumab without the use of any other systemic immunosuppressive medication.[72]

Table 3: Biologic therapies for the treatment of NIU. [69,70,71]

Class	Name
Anti-TNFα	Infliximab
	Adalimumab
	Golimumab
	Certolizumab
Anti-IL-1β	Anakinra
	Canakinumab
Anti-IL-2	Daclizumab
Anti-IL-6	Tocilizumab
	Sarilumab
Anti-IL-17A	Secukinumab
Anti-IL-12/ IL-23	Ustekinumab
Anti-CD20	Rituximab
Selective co-stimulator modulator	Abatacept
Interferons	IFN α-2a
	IFN α-2b
	IFN β
Janus kinase inhibitors	Tofacitinib
	Baricitinib
Other	Intravenous immunoglobulin

Biologic agents have enabled clinicians to avoid the long-term complications associated with chronic corticosteroid use and have given hope to those suffering from uveitis that has proven resistant to conventional immunotherapy. Tocilizumab, an IL-6 receptor antibody, in particular, is a new treatment option for uveitis and cystoid macular edema, and it has been used to treat chronic, refractory JIA-associated uveitis.[72] Rituximab, a chimeric anti-CD20 monoclonal antibody, has also shown promise in the treatment of a small group of patients with severe JIA who had previously failed conventional immunomodulatory therapy.[73]

A retrospective case series was recently conducted in 2023 to investigate the management trend of treating vogt-Koyanagi-Harada disease (VKH) over a 20-year period. Twenty-six patients were included, the study pointed to a shift in the last decade from steroid monotherapy to combined IMT/low-dose steroid for the management of acute VKH onset. this study showed average time between diagnosis and IMT initiationof 2.1 months. At 24

months, 81% (21 of 26 patients) of patients treated with combined IMT/steroid achieved disease stability with significant good visual outcome ($p = 0.0001$). Mycophenolate mofetil (MMF) monotherapy was the most commonly used IMT, and majority of patients tolerated it well. Despite this, 50% of MMF-treated patients did not achieve disease control. MMF was determined to be the most commonly used IMT, and it was well tolerated by the majority of patients in order to achieve disease remission and a good visual outcome with minimal VKH-related complications.[73] With the introduction of these promising therapies, additional prospective studies to determine optimal pediatric dosing regimens and safety profiles are required.[63]

Gene Therapy

Immunomodulatory gene therapy was studied in rats as a long-term treatment for noninfectious uveitis. From days 10 to 14, the investigators observed a significant (P.05) reduction in autoimmune uveitis scores and aqueous humor cell numbers in the eyes that received active treatment versus control eyes that received a saline injection in response to the intravitreal injections. The histologic inflammatory scores in the active-treatment eyes decreased significantly (P.05) when compared to the controls. The findings of vector genome biodistribution studies revealed that the AAV vector genomes remained in the ocular tissues, but the AAV capsid elicited a very low neutralizing antibody response.[74]

CONCLUSION

Uveitis diagnosis and management have come a long way in recent years. Because of advancements in imaging techniques, molecular diagnostic tools, and serologic testing, uveitis diagnosis has become more accurate and timelier. Individualized treatment plans, targeted therapies, and the use of biologic agents have transformed uveitis management, enabling better inflammation control and vision preservation.

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