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Ref: EMA updated 30 Oct 2014 (II-047+IB-048 Lucentis 04 Sep 2014)

1. Lucentis Product Information (Hong Kong) 2. Michaud JE, *et al.* Ranibizumab pre-filled syringe approved in the European Union: innovation to improve dose accuracy, reduce potential infection risk, and offer more efficient treatment administration. Poster presented at the Association for Research in Vision and Ophthalmology (ARVO 2014). 3. Souied E, *et al.* Ranibizumab pre-filled syringe versus single-use vial: syringe-preparation time in real-world clinical practice. Poster 256 presented at ESASO 2014 Istanbul, Turkey.

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1. *International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. ICMJE; April 2010. www.icmje.org*

香 港 眼 科 醫 學 院

THE HONG KONG JOURNAL OF OPHTHALMOLOGY
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To encourage submissions to the *Hong Kong Journal of Ophthalmology* (HKJO) by trainees and fellows of the College of Ophthalmologists of Hong Kong (COHK).

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Two awards will be given out every year. Each awardee will be given a $1000 cash prize (HK dollars), which is supported generously by the Timothy KC Liu Fund.

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- Applicants must be a paid-up member or fellow of COHK at the time of submission.
- Trainees refer to those who have not been conferred the title 'FCOphthHK' at the time of submission.
- Only the first author of the article will be eligible for the prize. If the first author is not eligible for the award, i.e. not a member of fellow of COHK, then the order of consideration of awardee will be from the second author onwards to the last author.
- Original articles (including, but not limited to, prospective or retrospective clinical studies, observational studies, epidemiological studies, basic science studies, meta-analysis, etc) published in the HKJO during the year will automatically enter the selection process.
- Case reports (with case number <3), review articles and letters to the editor will not be eligible for this award.
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- Methodology
- Presentation style

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EDITORIAL

香 港 眼 科 醫 學 院

Is there a role for prophylactic collagen crosslinking in laser *in-situ* keratomileusis?

Tommy CY Chan[*,1,2] *MBBS, MMedSc, FCOphth HK, FHKAM, FRCSEd, FRCS (Glasg), Alex LK Ng*[3] *MBBS, FCOphth HK, FHKAM, MRCSEd*

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Laser *in-situ* keratomileusis (LASIK) is one of the most common corneal refractive procedures. It involves lifting a corneal flap, ablation of the stromal bed with excimer laser to reshape the cornea, and re-placing the flap. Although LASIK has an excellent outcome and long-term safety record, iatrogenic ectasia and regression remain a concern, as lifting a flap and ablation of tissue inevitably weaken the corneal integrity. Such complications are more common following correction of high myopia, as more corneal tissue is ablated. Particularly in Hong Kong, there is a high prevalence of high myopia. Using swept-source optical coherence tomography, fluctuation of the posterior cornea during the first year following LASIK has been reported, demonstrating a possibility of postoperative corneal instability.[1]

Corneal collagen crosslinking (CXL) uses ultraviolet A (UVA) irradiation and riboflavin to induce crosslinks within the corneal stroma to increase the tensile strength and stability of the cornea.[2] It has been approved by the U.S. Food and Drug Administration for the treatment of keratoconus, which is an ectatic disorder due to biomechanical weakening of the cornea. The success of CXL in stabilizing keratoconus has led to its prophylactic application during LASIK (LASIK-CXL) to restore corneal biomechanical strength and prevent regression and ectasia.

In our review of 11 studies of LASIK-CXL in myopic and hyperopic eyes followed up for 1 month to 4.5 years,[3] outcome measures including postoperative manifest refraction spherical equivalent and uncorrected and corrected distance visual acuity (UDVA and CDVA) were evaluated following LASIK-CXL or LASIK. Compared with LASIK, LASIK-CXL achieved better efficacy (defined as the ratio of postoperative UDVA / preoperative CDVA) with a similar safety profile (defined as the ratio of postoperative CDVA / preoperative CDVA). Manifest refraction spherical equivalent after LASIK-CXL or LASIK showed no significant difference at a median follow-up duration of 12 months. A stronger inflammatory reaction and slight transient corneal haze was noted during the early postoperative period following LASIK-CXL. Nonetheless, no permanent side effects including corneal endothelial damage, stromal scarring or unintended flattening effect on keratometry were observed. Demarcation line, which indicates the crosslinking effect, was reported below the flap interface. It was harder to re-lift the flap during LASIK enhancement, indicating a stronger adhesion between the flap and the residual stromal bed. No iatrogenic ectasia developed following LASIK-CXL or LASIK.

In addition, we reported increased variance of postoperative

spherical equivalent and sphere in highly myopic eyes from 1 week up to 6 months after LASIK-CXL, compared with LASIK.[4] Transient delay in visual rehabilitation was also observed following LASIK-CXL. The increased variability in refractive outcome during the early postoperative period following LASIK-CXL may be due to an induced change in the healing process in the eyes.

There is no consensus on the optimal CXL protocol for LASIK-CXL. Following excimer stromal ablation, riboflavin solution is applied onto the stroma for 1-2 minutes with the flap lifted up. After residual riboflavin is thoroughly washed away, the flap is returned to its original position, and UVA irradiation performed. To save time, accelerated CXL protocols are adopted to shorten the irradiation duration by increasing the irradiation intensity to 10 to 30 mW/cm^2. The corresponding irradiation duration varies from 1 to 30 minutes with a total energy dose of 1.25 to 5.4 J/cm^2. These protocols are modified from the standard Dresden protocol for treating keratoconus that uses 5 mW/cm^2 for 30 minutes, with a total dose of 5.4 J/cm^2. We compared the early corneal morphological changes between two different protocols of LASIK-CXL in contralateral eyes.[5] There was no difference in the depth of stromal demarcation line or amount of postoperative corneal haze, despite a 50% difference in the irradiation duration as well as total energy dose. Insufficient diffusion of oxygen to fuel the photochemical reaction despite additional irradiation time may explain our observation.

There is a lack of studies of LASIK-CXL with sufficient patient numbers and follow-up duration. The main indication of LASIK-CXL is eyes at risk of iatrogenic ectasia or regression in patients with thin corneas or high refractive errors. The preliminary results are reassuring regarding the safety of the procedure. Stricter patient selection criteria, more long-term results and a standardized treatment protocol are needed to support the routine use of CXL in refractive surgery. LASIK-CXL has potential to improve the outcome of LASIK by restoring the biomechanical strength of the cornea, but it is still at an infant stage of development.

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Review Article

Update on the management of non-infectious uveitis

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Abstract

Uveitis is inflammation of the anterior, intermediate and/or posterior part of the uvea — the pigmented vascular coat of the eye. It can be infectious or non-infectious, idiopathic or secondary to systemic conditions. Uveitis has a wide range of presentations, from asymptomatic to rapidly sight-threatening disease, and can lead to permanent vision loss in the absence of early therapy. Ethnicity, genetics and the environment can account for regional variations in patterns of uveitis. Management of uveitis remains a challenge because of the diverse heterogeneity in presentation, and a paucity of randomized controlled trials evaluating different drug regimens. Despite being the mainstay of therapy for uveitis, corticosteroid monotherapy is increasingly viewed as unsuitable due to its significant side-effects. A stepwise approach is often adopted whereby least-to-more aggressive forms of therapy are trialed to induce remission. Treatment regimens are shifting from low-dose chronic corticosteroids for maintenance to medium-to-high-dose therapy to control acute inflammation, followed by rapid initiation of immunomodulatory therapy or biologics. This review provides a comprehensive overview of the challenges in managing patients with uveitis, as well as important advances in its investigations and treatment.

Key words: Uveitis; Uveitis, anterior; Uveitis, intermediate; Uveitis, posterior

Classification

Uveitis is intraocular inflammation of the uvea (including the iris, ciliary body and choroid), and may involve neighboring structures such as the retina, vessels, vitreous and optic nerve. Uveitis accounts for about 15% of preventable vision loss worldwide.[1] The most widely used classification of uveitis is devised by the International Uveitis Study Group and later amended by the Standardization of Uveitis Nomenclature working group, based on anatomic location of inflammation, inflammatory activity and etiology (**Tables 1-3**).[2,3] Most uveitis is anterior, but it can also be intermediate, posterior, or involve all layers (panuveitis). Uveitis can also be classified according to etiology: infectious or non-infectious (autoimmune or immune-mediated in origin).

Clinical presentations

Diagnosis of uveitis is challenging due to a wide range of etiologies. Delayed diagnosis may delay initiation of treatment with potentially serious consequences. Medical history taking should include ocular symptoms, onset, previous episodes, family history, social history (such as pets, travel abroad, drug use, sexual history), allergies or drug contraindications, and detailed systemic review. The onset of uveitis is usually acute, but it can follow a recurrent or chronic relapsing course (**Table 2**). Patterns of uveitis vary with race, genetic and environmental factors. For instance, Vogt-Koyanagi-Harada disease (VKH) and Behçet's disease are more common in Chinese than in Caucasians.[4,5] Associations with sarcoidosis and multiple sclerosis (MS) are less common in Chinese.[6]

Patients with anterior uveitis may present with redness, periorbital pain, photophobia, and blurred vision. Slit lamp findings are conjunctival injection, ciliary flush in the perilimbal area, anterior chamber cells or flare, and keratic precipitates. Recurrent attacks or untreated anterior uveitis can result in posterior synechiae, secondary cataract

Table 1. Classification of uveitis.[3]		
Uveitis type	**Primary site of inflammation**	**Involvement**
Anterior	Anterior chamber	Iritis, iridocyclitis, anterior cyclitis
Intermediate	Vitreous	Pars planitis, posterior cyclitis, hyalitis
Posterior	Retina or choroid	Choroiditis (focal/ multifocal/ diffuse), Chorioretinitis/retinochoroiditis, retinitis, neuroretinitis
Panuveitis	Anterior chamber, vitreous and retina/choroid	All intraocular structures

Table 2. Clinical presentation of uveitis.[3]	
Presentation	**Description**
Onset	
Sudden/insidious	-
Duration	
Limited	≤3 months
Persistent	>3 months
Course	
Acute	Sudden onset + limited duration
Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 months
Chronic	Persistent uveitis with relapse in <3 months after stopping treatment

Table 3. Etiological classification of uveitis.[2]
Etiology
Infectious
Bacterial
Viral
Fungal
Parasitic
Others
Non-infectious
Known systemic association
No known systemic association
Masquerade
Neoplastic
Non-neoplastic

or glaucoma, corneal endothelial loss, macular edema, and band keratopathy. Non-infectious anterior uveitis should be differentiated from anterior uveitis caused by the herpes viruses (herpes simplex, varicella zoster and cytomegalovirus; including Posner-Schlossman syndrome). Viral anterior uveitis presents with raised intraocular pressure (IOP), patchy iris atrophy, pigmented keratic precipitates, endothelial cell loss, corneal edema and absence of anterior or posterior synechiae. Viral anterior uveitis requires antiviral treatment.[7]

Major histocompatibility complex HLA-B27-associated uveitis is the most common type of anterior uveitis (in up to 50% of cases), especially in males or those with a positive family history. Patients with ankylosing spondylitis and Reiter's syndrome are frequently HLA-B27 positive. HLA-B27-associated uveitis usually presents in young individuals as severe inflammation, often associated with a fibrinous reaction, a hypopyon, posterior synechiae, and more frequent recurrences.

Intermediate uveitis commonly presents with floaters and blurred vision. Pars planitis is a subset of intermediate uveitis associated with snowbank and snowball formation in the absence of infectious or systemic disease. It predominantly affects children and adolescents. Typical findings are diffuse vitreous cells, snowballs and snowbanks, peripheral retinal venule sheathing or frank retinal vasculitis, and optic disc edema. Other signs include anterior segment inflammation, posterior synechiae, and peripheral corneal endotheliopathy. Complications include band keratopathy (in up to 45% of affected eyes, and a hallmark of childhood pars planitis), cataract, cystoid macular edema, epiretinal membrane, vitreous opacities, retinal neovascularization, vitreous hemorrhage, retinal tears or detachment, cyclitic membranes, or glaucoma. Intermediate uveitis has a strong association with MS in Caucasians, but the incidence is lower in Chinese. Prominent retinal periphlebitis or optic neuritis should prompt magnetic resonance imaging of the brain and cerebrospinal fluid analysis.

Patients with posterior uveitis may be asymptomatic (often in children) or present with floaters due to vitreous involvement, photopsia, and blurred vision. Fundal examination may reveal moderate to dense vitritis, retinal vasculitis, cotton wool spots, perivascular sheathing, inflammatory exudates, and retinal hemorrhage. Inflammation in posterior uveitis can also cause retinal, macular or optic disc edema. Complications include secondary cataract or glaucoma, chorioretinal scars, retinal neovascularisation, epiretinal membranes, retinal detachment, optic disc atrophy, permanent vision loss or phthisis. Prompt diagnosis and initiation of therapy are important to avoid these serious complications.

Most non-infectious uveitis is idiopathic in nature, but can also be secondary to systemic rheumatological diseases. Uveitis is the most frequent extra-articular manifestation in spondyloarthritis (including psoriatic arthritis and ankylosing spondylitis), and often precedes systemic involvement.[8,9]

Anterior uveitis affects about 10-20% of children with juvenile idiopathic arthritis, is more prevalent in girls, in the oligoarticular subtype, and typically has an indolent and chronic course.[10] About 30-70% of patients with Behçet's disease develop uveitis, typically as a chronic relapsing bilateral panuveitis, with a more severe clinical course in males, and with younger age of onset. About 25% of patients with retinal involvement develop severe sequelae (including vascular thrombosis, hemorrhage and macular edema) leading to blindness.[11] Relapsing polychondritis, a rare condition of recurrent inflammation of cartilage (affecting ears, nose, trachea and larynx), can cause uveitis and scleritis. Uveitis is also associated with other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), polyarteritis nodosa (PAN), and inflammatory bowel disease. Systemic clues may prove valuable to diagnosis and should be actively sought and ruled out (**Table 4**).

Other systemic conditions may also be associated with uveitis. Sarcoidosis can present as a chronic granulomatous uveitis with mutton fat keratic precipitates, iris nodules, posterior synechiae, and cystoid macular edema. Pulmonary

Table 4. Systemic symptoms of underlying disease.

Site/symptoms	Underlying disease
Central nervous system, head & neck	
Headaches	Vogt Koyanagi Harada (VKH), sarcoidosis, Behçet disease, tuberculosis (TB), herpes zoster virus (HZV), large cell lymphoma, polyarteritis nodosa (PAN), cryptococcus meningitis, toxoplasmosis
Auditory/vestibular	VKH, sarcoidosis, granulomatosis with polyangiitis (GPA), Eale's disease, syphilis
Cranial neuropathy	Sarcoidosis, multiple sclerosis, syphilis, herpes simplex virus (HSV)
Cerebral vasculitis	Acute posterior multifocal placoid pigment epitheliopathy (APMPPE), Behçet disease, HSV, HZV, syphilis
Sinusitis	GPA, Sarcoidosis
Oral ulcers	Behçet disease, systemic lupus erythematosus (SLE), HSV, Reiter syndrome, ulcerative colitis
Lymphadenopathy	Lymphoma, human immunodeficiency virus (HIV), toxoplasmosis
Dermatological	
Alopecia	VKH, syphilis
Vitiligo	VKH
Skin nodules	Sarcoidosis, SLE, leprosy, Crohn's disease, ulcerative colitis
Erythema nodosum	Behçet disease, sarcoidosis
Keratoderma blennorrhagicum	Reiter syndrome, ankylosing spondylitis
Musculoskeletal	
Arthralgias/arthritis	Behçet disease, sarcoidosis, SLE, juvenile idiopathic arthritis, Lyme disease, syphilis, psoriatic arthritis, Reiter syndrome, ulcerative colitis
Sacroiliitis	Ankylosing spondylitis, Reiter syndrome, inflammatory bowel disease
Genitourinary	
Genital ulcers	Behçet disease, Reiter syndrome, syphilis
Hematuria	GPA, PAN, SLE
Circinate balanitis	Ankylosing spondylitis, Reiter syndrome
Urethral discharge	Reiter syndrome, syphilis
Nephritis	PAN, GPA, tubulointerstitial nephritis and uveitis
Epididymitis	PAN, Behçet disease, Reiter syndrome
Gastrointestinal	
Diarrhea	Crohn disease, ulcerative colitis, HIV
Blood/mucus in stool	Behçet disease, Crohn's disease, ulcerative colitis, HIV
Jaundice	Toxoplasmosis, autoimmune hepatitis, infectious hepatitis
Pulmonary	
Cough	TB, sarcoidosis, Pneumocystis carinii pneumonia, malignancy, GPA
Nodules, hilar adenopathy, infiltrates	Ocular histoplasmosis, sarcoidosis, malignancy, TB, pneumocystis carinii pneumonia
Constitutional	
Fever	Reiter syndrome, Behçet disease, PAN, inflammatory bowel disease, TB, coccidioidomycosis
Night sweats	Malignancy, TB, sarcoidosis, coccidioidomycosis
Flu-like symptoms	APMPPE, multiple evanescent white dot syndrome

and central nervous system involvement, polyarthritis and erythema nodosum are typical systemic findings. Vogt-Koyanagi-Harada syndrome is a systemic autoimmune disease characterized by neurological, auditory and dermatological involvement and bilateral, chronic, granulomatous panuveitis. It is more common among Chinese and Japanese patients. Tubulointerstitial nephritis and uveitis is rare, typically affects young females, and can cause acute renal failure, as well as recurrent or persistent anterior uveitis. Other syndromes can be restricted to the eye. Birdshot chorioretinopathy presents as bilateral posterior uveitis, and is characterized by multiple, hypopigmented areas of chorioretinitis. Sympathetic ophthalmia is a rare bilateral granulomatous panuveitis that occurs in the 'sympathizing eye' following penetrating injury or surgery to the other eye.

Investigations

As most cases of acute anterior uveitis are idiopathic, investigations may have a low diagnostic yield and may not be required for the first episode of isolated unilateral, mild to moderate, acute anterior non-granulomatous uveitis that responds to treatment. Nonetheless, investigations are helpful for diagnosis and monitoring of disease activity or complications and adverse effects of treatment. Initial investigations include complete blood count (CBC) with differential, erythrocyte sedimentation rate, chest radiography to exclude tuberculosis (TB) and sarcoidosis, and screening for infectious agents such as syphilis.[12] Depending on other ocular and systemic findings (**Tables 4 and 5**), selective investigations include autoimmune serology such as rheumatoid factor, antinuclear antibody, c- and p-antineutrophil cytoplasmic antibodies for GPA, PAN, toxoplasma serology, viral polymerase chain reaction (PCR) of intraocular fluid, radiographs of the lumbosacral spine for ankylosing spondylitis, HLA-B27 in severe anterior uveitis, HLA-A29 for birdshot chorioretinopathy, and angiotensin-converting enzyme levels for sarcoidosis. Birdshot chorioretinopathy and sarcoidosis are rare in Chinese. Hepatitis B serology is commonly ordered in Hong Kong due to the higher prevalence of hepatitis B. Flare up of viral hepatitis can occur during tapering of systemic steroids or with administration of biologics, and requires concomitant antiviral medication.

It is important to exclude viruses and TB as causes of uveitis. PCR analysis of aqueous or vitreous for viral DNA is helpful in confirming the diagnosis of viral uveitis and quantifying viral load. The Goldmann-Witmer coefficient compares the level of intraocular antibody production against the virus to that of the serum; a coefficient >3 is considered positive for active intraocular antibody production to a specific viral pathogen. It is a useful test but not widely performed by

Table 5. Differential diagnosis of uveitis.

Anatomic location/onset	Differential diagnosis
Anterior	
Acute and severe	Behçet's disease, seronegative arthropathies, idiopathic
Acute and moderate severity	Viral uveitis, syphilis, related to intraocular lens implant, Posner-Schlossman syndrome
Chronic, mild severity	Juvenile rheumatoid arthritis, Fuchs heterochromic iridocyclitis, viral uveitis, related to intraocular lens implant, chronic postoperative endophthalmitis (e.g. propionibacterium acnes)
Intermediate	Idiopathic, syphilis, tuberculosis (TB), human T-cell lymphotropic viruses, multiple sclerosis, Sjogren's syndrome, sarcoidosis, intraocular lymphoma
Chorioretinitis with vitritis	
Focal	Cytomegalovirus retinitis, toxoplasmosis, toxocariasis
Multifocal	Acute retinal necrosis or progressive outer retinal necrosis, TB, immunosuppressed (candidasis, toxoplasmosis, syphilis), sarcoidosis, intraocular lymphoma, birdshot retinochoroidopathy, idiopathic (multifocal choroiditis with panuveitis), onchocerciasis, cysticercosis
Diffuse	As panuveitis below
Chorioretinitis without vitritis	
Focal	Neoplasia
Multifocal	White dot syndromes, serpiginous choroiditis, ocular histoplasmosis
Diffuse	Onchocerciasis
Panuveitis	Vogt-Koyanagi-Harada disease, sympathetic ophthalmia, sarcoidosis, syphilis, toxoplasmosis endophthalmitis, toxocariasis, cysticercosis
Retinal vasculitis	
Veins	Behçet's syndrome, sarcoidosis, multiple sclerosis
Arteries	Systemic lupus erythematosus, granulomatosis with polyangiitis polyarteritis nodosa
Arteries and veins	Crohn's disease, relapsing polychondritis
Capillaries	Whipple's disease

laboratories.[13,14]

TB as an infectious cause of uveitis is less common in Hong Kong, owing to the almost universal neonatal Bacillus Calmette-Guerin (BCG) vaccination program. TB has been a notifiable disease since 1939. The direct observed treatment strategy is implemented for active cases. Ocular TB is difficult to diagnose, and criteria for tuberculous uveitis include residence or migration from endemic areas, suggestive ocular findings, positive tuberculin skin test (TST), positive interferon-gamma release (IGR) assay, and positive treatment response. Extraocular evidence of TB aids in the diagnosis of ocular TB.[15] The classic Mantoux test consists of an intradermal injection of 5 units of purified protein derivative. False positive can occur with exposure to non-tuberculous mycobacteria, previous BCG vaccination, and in patients with exaggerated skin hypersensitivity, as in Behçet's disease. False negative TST can occur in the elderly and immunosuppressed. QuantiFERON-TB Gold and T-SPOT TB blood tests are based on the detection of IGR by T cells sensitized to TB-specific antigens, and thus are not influenced by BCG and non-tuberculous mycobacteria. IGR assays are more expensive and require blood processing. They are more specific and sensitive than TST in detecting active pulmonary TB, but are less sensitive than TST in diagnosing latent TB. T-SPOT TB is more specific for diagnosing TB-associated uveitis, and is a better diagnostic tool when used as an adjunct to TST.[15] Recently, PCR has emerged as a highly specific diagnostic test for ocular TB. Nonetheless, it is not routinely used as it requires larger volumes of vitreous compared with that required for viral testing, has variable sensitivity and may require repeat invasive testing.[16]

Diagnostic vitreous biopsy may be necessary where masquerade syndromes, such as primary ocular lymphoma, are a possibility, or when the initial workup is inconclusive. Severe vitritis, chorioretinal lesions and poor-to-partial response to therapy may be clues to primary intraocular lymphoma. A high level of interleukin 10, or an interleukin-10-to-6 ratio >1 in the aqueous humor or vitreous is suggestive of primary intraocular lymphoma.[17,18] To improve yields from vitreous samples, steroids should be stopped 2 weeks prior to sampling, and undiluted vitreous samples should be obtained by vitrectomy rather than a vitreous tap. If delivery to the laboratory and rapid processing of fresh unfixed vitreous samples cannot be achieved within 1 hour of acquisition, which is often the case in clinical practice, use of fixatives such as PreservCyt or CytoRich in transport media allows preservation of cell architecture for morphological examination, immunohistochemistry, and molecular genetic tests for clonality assessment with PCR.[19-21] Magnetic resonance imaging of the brain, cerebrospinal fluid analysis, and the presence of neurological symptoms may also help in the diagnosis of primary central nervous system lymphoma, which may be associated with primary intraocular lymphoma.

Ultrasound biomicroscopy is valuable in assessing the ciliary body and pars plana. Ultrasonography is useful in evaluating uveitis, especially when fundus visualization is poor due to media haze. It can assess the extent and density of vitritis, and detect posterior vitreous detachment, low-to-medium reflective diffuse choroidal thickening in acute VKH, high-reflective sclera-choroidal thickening in diffuse posterior scleritis, and echolucent 'T' sign due to scleral edema associated with fluid in Tenon's space just posterior to the sclera.[22]

Retinal imaging

Fundus photography, fundus fluorescein and indocyanine green angiography, fundus autofluorescence, and optical coherence tomography (OCT), are useful in diagnosis and monitoring of clinical course and therapeutic response in uveitis.

OCT creates high-resolution images by using time-of-flight delays and interference patterns of infrared light from reference and sample beams of light backscattered from ocular tissues. Spectral-domain OCT provides 5-7 μm axial resolution. In uveitis, OCT can distinguish four distinct subtypes of macular edema: diffuse macular edema, cystoid macular edema, serous retinal detachment, or thickening due to vitreoretinal interface abnormalities such as an epiretinal membrane (up to 50% in uveitis).[23,24] OCT is therefore useful to guide surgical intervention in eyes with vitreomacular traction. Uveitic macular atrophy is defined by Forooghian as central foveal thickness <150 μm, reduced photoreceptor outer segment length, and/or partial or total disruption of the inner/outer segment junction.[25] Disruption of the ellipsoid zone of the photoreceptor outer segments has been negatively correlated with visual acuity, and is an important predictor of final visual acuity and response to treatment in uveitic macular edema. In multiple evanescent white dot syndrome, OCT findings are inner/outer segment disruption, preserved external limiting membrane, and focal hyperreflective lesions in the photoreceptor layer. OCT can detect and monitor subclinical disease activity in punctate inner choroidopathy complicated by choroidal neovascularization or recurrent inflammatory activity.

Choroidal imaging was first used with spectral-domain OCT using enhanced depth imaging to position the choroid closer to the 'zero-delay line' by obtaining an inverted image. Swept-source OCT avoids scattering by the retinal pigment epithelium, and penetrates deeper than spectral-domain OCT to provide high-resolution cross-sectional images of the whole thickness of the choroid (from Bruch's membrane to the choriocapillaris, Sattler layer, Haller layer, and lamina suprachoroidea). In VKH, retinal pigment epithelium undulations (due to choroidal inflammation and congestion), and choroidal thickness (thicker in the acute phase than the convalescent phase) are useful in diagnosis and monitoring therapeutic response.[26]

Fundus fluorescein angiography is useful to differentiate active from inactive uveitis, and in the diagnosis of cystoid

macular edema, choroidal neovascularization, retinal vasculitis, neovascularization, and ischemia. Ultra-wide field fluorescein angiography can detect changes in the peripheral retina in posterior uveitis, especially vasculitis, leakage, neovascularisation and capillary non-perfusion, which are often missed by conventional fluorescein angiograms. It is therefore useful to guide therapy such as targeting laser to areas of ischemia.[27,28]

Fundus autofluorescence uses a confocal scanning laser ophthalmoscope to detect autofluorescence produced by fluorophores (such as lipofuscin), which originate from photoreceptor outer segment and accumulate in retinal pigment epithelium cells.[22] It indicates the metabolic state of the retinal pigment epithelium, and may reflect disease activity. It shows hyperautofluorescence at the borders of active edges in serpiginous choroiditis, and at the borders of hypoautofluorescent placoid lesions in acute posterior multifocal placoid pigment epitheliopathy. Hypoautofluorescent lesions in acute zonal occult outer retinopathy correspond to zonal loss of photorceptors.[29]

Treatment for non-infectious uveitis

Anterior uveitis

Acute, non-infectious anterior uveitis can be treated with local corticosteroids and dilating eye drops to break posterior synechiae.[30] Intensive topical corticosteroids are usually effective, but subconjunctival dexamethasone may be required in severe inflammation with fibrinous reaction to help prevent posterior synechiae. Topical corticosteroids are tapered according to therapeutic response. Topical or systemic anti-glaucomatous drugs may be useful to control any rise in IOP secondary to uveitis or steroids. Non-steroidal anti-inflammatory drugs (NSAIDs) may be considered as steroid-sparing agents, or if there is associated macular edema. If all treatments fail to control inflammation or if prolonged topical steroids are required, systemic corticosteroids or immunomodulatory agents should be considered. Cataract surgery or lysis of posterior synechiae may sometimes need to be performed in these eyes, but a high risk of uveitis relapse should be anticipated. Relapse can be prevented using perioperative corticosteroids with slow tapering, meticulous surgical technique, as well as intracameral or subconjunctival dexamethasone.

Intermediate or posterior uveitis

After excluding underlying diseases and masquerade syndromes, corticosteroids may be administered as first-line treatment. Vitreous haze leading to decreased visual acuity, macular edema, vasculitis, snowbanking, or complications such as band keratopathy or cataract are indications for treatment. A stepwise approach to treatment is suggested. Topical steroids are used if there is anterior segment inflammation, but they do not achieve adequate therapeutic levels in the posterior segment, especially in phakic eyes. Hence, systemic or periocular steroids are required as first-line treatment in most patients. Steroid-sparing immunosuppressive therapy is usually the second step in patients who require long-term treatment, but may be considered as a primary therapy in aggressive uveitis. Methotrexate (especially in children), azathioprine, mycophenolate mofetil, and cyclosporine may be used individually or in combination. Anti-tumor necrosis factor (TNF)-α, such as infliximab and adalimumab, is useful as the third step in those not responding to conventional immunosuppressive drugs. Alkylating agents are less frequently given due to potentially serious side effects. Vitrectomy is the fourth step, especially in patients with complications such as dense vitreous condensations, epiretinal membrane, vitreous hemorrhage, retinal detachment, or refractory cystoid macular edema. Laser therapy should be considered as adjunctive therapy to treat peripheral retinal neovascularization. Cataract surgery may be needed, preferably when inflammation has been controlled for at least 3 months. Systemic corticosteroids should be given prior to surgery, in addition to any other systemic immunosuppressive therapy, followed by intensive topical steroids in the postoperative period. Alternatively, periocular steroids or an intravitreal steroid implant may also be considered at the time of cataract surgery.[31,32]

A general algorithm for the treatment of patients with non-infectious uveitis is shown in the **Figure**. Guidelines for the use and monitoring of immunosuppressive drugs in ocular inflammatory disease were published by a uveitis expert panel in 2000.[33] Since then, the evidence for steroid-sparing agents in uveitis has grown, and updates in treatment are discussed below.

Common drugs used for uveitis

Corticosteroids

Corticosteroids block phospholipase A2, thereby inhibiting prostaglandin production through the cyclooxygenase pathway, and leukotriene production through the lipooxygenase pathway. Corticosteroid monotherapy carries significant side effects, especially with increasing dose and duration. Treatment regimens have therefore shifted away from low dose chronic corticosteroids for maintenance to medium-to-high dose to control acute inflammation, followed by rapid initiation of immunomodulatory therapy or biologics for long-term control.

Periocular steroids, usually in the form of subtenon injections of triamcinolone acetonide (superotemporally) or orbital floor injections of triamcinolone or methylprednisolone acetate (retroseptally through the lower lid), are useful in unilateral intermediate or posterior uveitis, and in the presence of macular edema. Complications include increased IOP, cataract, aponeurotic ptosis (for subtenon injections), orbital fat prolapse (for orbital floor injections), and rarely periorbital hemorrhage or globe perforation.[34-36] Intravitreal steroids such as preservative-free triamcinolone (Triesence; Alcon, USA) can also be considered. Nonetheless, higher rates of complications can occur, including cataract, increased IOP, glaucoma, vitreous hemorrhage, retinal detachment and endophthalmitis. Ozurdex (Allegan, Irvine, CA, USA),

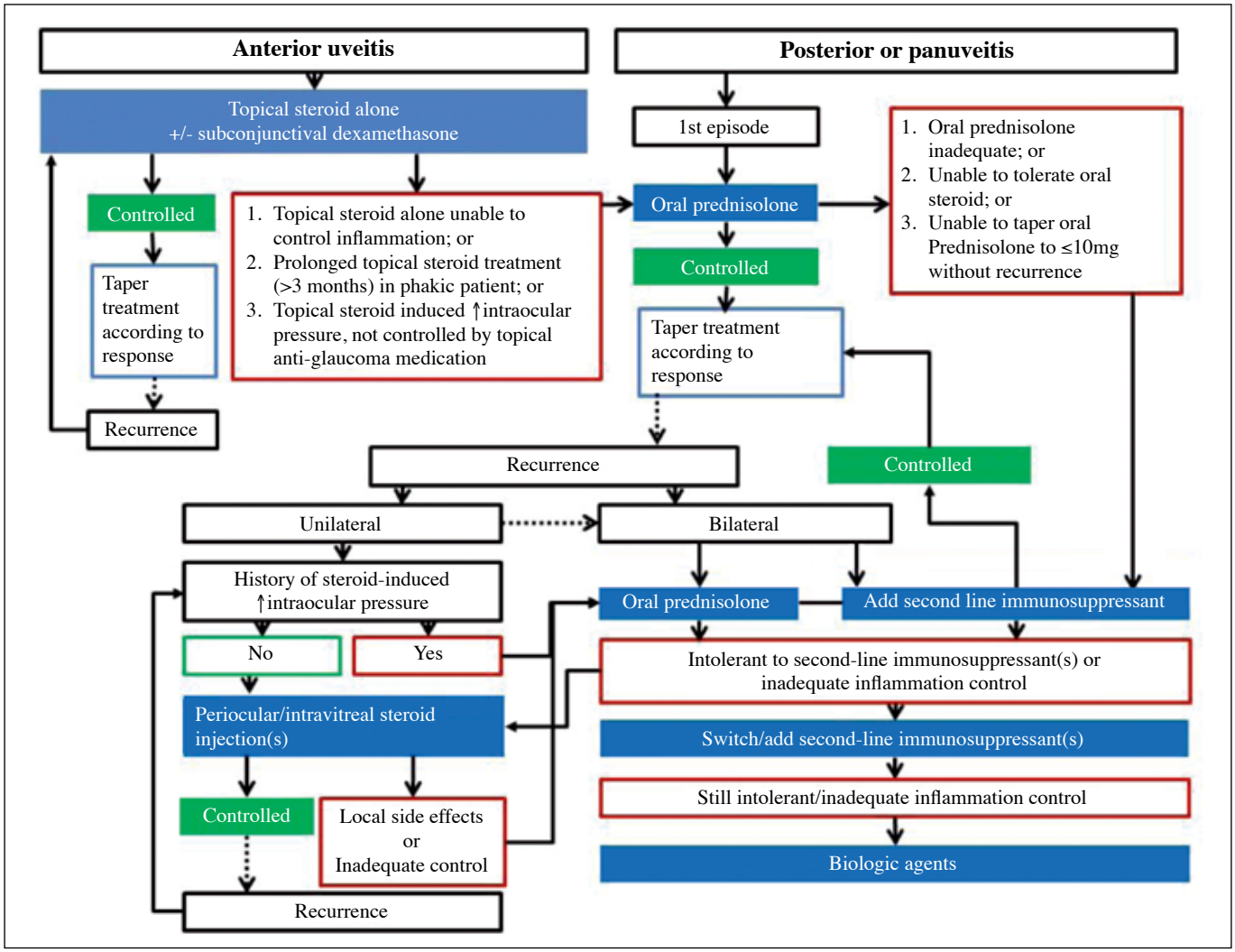

Figure. Management flowchart for non-infectious uveitis*.
* Second-line immunosuppressants include methotrexate, azathioprine, mycophenolate, cyclosporine and cyclophosphamide, whereas biologic agents include adalimumab and infliximab

a 0.7 mg intravitreal dexamethasone implant, can be used in intermediate and posterior uveitis, with effects lasting 3 to 6 months. Retisert (Bausch & Lomb) is a corticosteroid implant (with 0.59 mg fluocinolone acetonide) which is associated with high rates of glaucoma and cataract. Iluvien (Alimera Sciences), a 0.19 mg fluocinolone acetonide implant, is still undergoing clinical trials.[37,38]

Systemic steroids should be considered in patients with bilateral involvement, severe uveitis, lack of response or contraindications to periocular steroids. The most widely used systemic steroids for uveitis are oral prednisolone and intravenous methylprednisolone. Prednisolone is usually initiated at a dose of 1-1.5 mg/kg/day, while intravenous methylprednisolone is dosed at 500-1000 mg/day for 1-3 days followed by oral prednisolone, and tapered by 5-10 mg a week according to clinical response until the lowest dose for maintenance. Systemic steroids are associated with systemic side effects in almost all organ systems, including hypertension, diabetes, hyperlipidemia, leukocytosis, hypokalemia, adrenal insufficiency, peptic ulcer, osteoporosis, myopathy, avascular necrosis of the hip, weight gain, Cushingoid habitus, acne, hirsutism, menstrual irregularities, insomnia, psychosis and growth retardation in children. Periodic monitoring of blood pressure, body weight, blood glucose, lipids, CBC, liver and renal function tests are necessary. Histamine-2 receptor blockers or proton pump inhibitors should be prescribed in conjunction with oral corticosteroids, and clinicians should be aware that prescribing concurrent systemic NSAIDs may increase the risk of gastric ulcers.[39,40] Patients prescribed oral corticosteroids for >3 months, especially postmenopausal women, should have supplemental calcium and vitamin D to minimize the risk of osteoporosis, and have bone mineral density monitored with dual X-ray absorptiometry.[39] Abrupt steroid discontinuation should be avoided, as it may lead to flare up of uveitis, and viral hepatitis flare up in hepatitis B carriers.

Non-steroidal anti-inflammatory drugs

NSAIDs inhibit prostaglandin synthesis in the arachidonic acid pathway by blocking cyclooxygenase isoforms 1

and 2 or 2 alone. Topical NSAIDs (including ketorolac, diclofenac, nepafenac and flurbiprofen) are useful for uveitic cystoid macular edema and postoperative inflammation, but may rarely cause corneal melting in the presence of epithelial defects in compromised corneas of patients with diabetes, history of herpetic disease, or ocular surface disease. Systemic NSAIDs (including naproxen and ibuprofen) are useful as steroid-sparing agents in recurrent idiopathic or HLA-B27-associated anterior uveitis, as they reduce recurrence rates and cumulative effects of steroids. Complications of NSAIDs include gastrointestinal reflux, bleeding or ulceration, hypertension, renal and hepatic toxicity. Selective cyclooxygenase-2 inhibitors, such as celecoxib, have fewer gastrointestinal side effects, but may be associated with increased risk of cardiovascular thrombotic events.[41]

Immunomodulatory agents

A stepwise approach in applying corticosteroid-sparing immunomodulatory therapy to achieve durable, corticosteroid-free remission is the standard of care.[40] Immunomodulatory therapy is indicated for acute non-infectious uveitis that is refractory to high-dose corticosteroids for >2 weeks, inability to taper down prednisolone (to <10 mg/day), or poor tolerance of steroid side effects.[42] In patients with potentially lethal disease, such as PAN, GPA, Behçet's disease or systemic lupus erythematosus with retinal vasculitis, rheumatoid arthritis or relapsing polychondritis with new onset necrotizing scleritis, aggressive and immediate treatment with immunomodulatory drugs should be considered, and then transitioning to biologics with remission >6 months.[41]

The main action of immunosuppressants is widespread suppression of lymphoid proliferation. Based on their specific mechanism of action, they are subdivided into: antimetabolites, alkylating agents, and antibiotics and calcineurin inhibitors (**Table 6**). Selecting the optimal immunomodulatory agent to begin therapy is difficult and requires a multidisciplinary approach liaising with rheumatologists, internists and pediatricians to administer and monitor therapy. Special attention is paid to the type and severity of uveitis, patient age, sex, compliance, medical and social history, and type of family planning. Thorough informed consent, including detailed discussion of the potential risks and benefits of the different agents, is imperative to ensure safety and efficacy therapy. CBC (including differential), liver and renal function tests, and urinalysis should be performed prior to therapy, and at 1-4 week intervals. Periodic monitoring for treatment efficacy and toxicity is required, and patients are generally followed up every 2 months. As immunosuppressed patients are at increased risk of infection, they should be warned to seek urgent medical attention for fever or sore throat.

Antimetabolites

Methotrexate, an inhibitor of dihydrofolate reductase, inhibits DNA replication. It has a moderate immunosuppressive effect, excellent tolerance and side-effect profile, and is particularly useful in children. It can be administered via oral, subcutaneous, intramuscular, intravenous, and intravitreal routes, with higher bioavailability via parenteral routes. Effect via systemic routes takes 6-8 weeks to occur. In the SITE study of multicenter collaborative systemic immunosuppressive therapy for eye diseases, methotrexate produced corticosteroid-free remission in 66% of patients within 1 year, with only 16% discontinuing due to side effects (**Table 6**), all of which were reversible with cessation of methotrexate. Folic acid supplementation (1 mg/day other than methotrexate dosing day) should be prescribed.[43] Intravitreal methotrexate at a dose of 400 μg is a safe and efficacious alternative to regional corticosteroids for treating unilateral uveitis and uveitic cystoid macular edema, especially in steroid responders. Rapid onset of effect occurs within a week, and extended remission in 73% of patients can be induced by a single intravitreal injection of methotrexate.[44,45]

Azathioprine inhibits purine metabolism, and takes about 4-12 weeks for effect. Control of inflammation is most commonly achieved in patients with intermediate uveitis. Thiopurine methyltransferase genetic polymorphisms have been associated with azathioprine-induced myelosuppression from the accumulation of toxic metabolites. Patients should therefore be tested for thiopurine methyltransferase enzyme, and doses adjusted accordingly. Vigilant blood monitoring is crucial to detect myelosuppression.

Mycophenolate mofetil selectively inhibits B and T cell lymphocytes, and therefore may have fewer and milder side effects. It is less convenient to use than methotrexate, as it must be taken orally daily on an empty stomach. Effect takes 3 to 6 weeks to occur. An enteric form of mycophenolic acid, Myfortic, was developed with the intent of reducing the incidence of gastrointestinal side effects. Antimetabolites are typically maintained for 2 years to achieve durable steroid-free remission. Studies have not shown increased cancer risk or mortality with antimetabolites.

Antibiotics and calcineurin inhibitors

Cyclosporine, a fungal metabolite, specifically inhibits T-lymphocyte signaling by inhibition of calcineurin. It is fast-acting and takes 7-15 days for effect. Hypertension and transient renal impairment are the most common side effects. Toxicity occurs more often in older patients, in whom alternative immunosuppressants are preferred. Cyclosporine is effective in Behçet's disease, VKH and sarcoidosis. It can be used in combination with mycophenolate mofetil in birdshot chorioretinopathy, or with methotrexate and NSAIDS in juvenile idiopathic arthritis–associated uveitis.[46] Therapy is usually continued for 2 years to obtain steroid-free remission.

Sirolimus, a macrolide antibiotic, inhibits mammalian target of rapamycin and subsequent inflammatory cascade that leads to T cell activation and proliferation.[47] It can be delivered via oral, intravitreal and subconjunctival routes. Subconjunctival and intravitreal sirolimus is well

Table 6. Second-line immunosuppressants.

Drug	Route	Dose	Mechanism	Side effects	Supplement
Antimetabolites					
Methotrexate	Oral/intramuscular/ intravenous/ intravitreal	7.5-25 mg/week (oral)	Inhibits dihydrofolate reductase	Gastrointestinal intolerance, bone marrow suppression, liver toxicity, pulmonary fibrosis, phototoxicity	Folic acid weekly, not on same day as methotrexate administration (e.g. 5 mg 2 days after methotrexate)
Azathioprine	Oral	50-150 mg/day (2 mg/kg)	Inhibits purine metabolism	Gastrointestinal intolerance, bone marrow suppression, liver toxicity	Pretreatment: check thiopurine methyltransferase level (low levels increase risk of myelosuppression)
Mycophenolate mofetil	Oral	500-1500 mg bd/day	Inhibits purine metabolism	Gastrointestinal disturbance, bone marrow suppression, liver toxicity	H2-receptor antagonist
T-lymphocyte signaling inhibitors					
Cyclosporine	Oral	2-5 mg/kg/day	Transcription factor inhibitor: inhibits calcineurin	Bone marrow suppression, nephrotoxicity, hepatotoxicity, hypertension, gingival hyperplasia, hirsutism	-
Sirolimus	Oral/ subconjunctival/ intravitreal	If body weight ≥40 kg, oral loading: 6 mg/day; maintenance: 2 mg/day	Inhibition of mammalian target of rapamycin: inhibits cytokines	Nephrotoxicity, hepatotoxicity, hypertension	-
Alkylating agents					
Cyclophosphamide	Oral/intravenous	2-3 mg/kg/day	Inhibition of DNA crosslinking & cell replication	Bone marrow suppression, hemorrhagic cystitis, gastrointestinal disturbance	-

tolerated.[48] Tacrolimus is another macrolide antibiotic with similar efficacy, and more favorable side effect profile than cyclosporine, but experience in uveitis is limited.

Alkylating agents

Alkylating agents are some of the most potent but toxic agents available to control uveitis. Cyclophosphamide, an analog of nitrogen mustard, inhibits DNA and RNA function and synthesis, and has effects throughout the cell cycle, resulting in profound effects on B and T cells. It is usually restricted to severe sight-threatening and refractory uveitis, and takes about 2-8 weeks for effect. The SITE study showed 81% of patients achieved remission within 1 year, but 34% discontinued treatment due to side effects. Cyclophosphamide is effective in scleritis associated with underlying PAN, GPA, rheumatoid arthritis, and relapsing polychondritis. Myelosuppression is the most common side effect, and is reversible with cessation. Hemorrhagic cystitis due to acrolein build-up can occur with inadequate hydration, and patients are encouraged to drink ≥2 L of water daily. Regular CBC and urinalysis are required.

Chlorambucil primarily affects B cells, takes 4-12 weeks to achieve effect, and has similar side effect profile to cyclophosphamide. It has been used in Behcet's disease, HLA-B27-associated uveitis, pars planitis and sympathetic ophthalmia. Myelosuppression, whilst usually reversible, may progress to irreversible aplastic anemia. Nonetheless, alkylating agents are associated with increased malignancy risk, including bladder cancer (most common), leukemia, lymphoma, and skin cancer. Treatment is therefore limited to ≤1 year.

Biologics

Biologic response modifiers are monoclonal antibodies or other proteins produced by recombinant DNA technology that specifically target cytokines or their signaling pathways. The biologics most widely used for treating uveitis are the TNF-α inhibitors, infliximab and adalimumab. They are effective in Behçet's disease, and uveitis associated with juvenile idiopathic arthritis, GPA, and sarcoidosis. Recent recommendations from the American Uveitis Society suggest use of biologics as first-line therapy in Behçet's disease, and as a potential second-line agent in other severe or resistant uveitis. Nonetheless, biologics are expensive and so far only adalimumab is approved by the US Food and Drug Administration for the treatment of non-infectious uveitis.

Infliximab (Remicade), a chimeric monoclonal antibody, is given by intravenous infusion at a dose of 5-10 mg/kg at weeks 0 and 2, followed by maintenance dose every 4-8 weeks, depending on inflammation control. Most patients show improvement in inflammation after the second infusion, and the treatment is generally continued for 2 years to achieve steroid-free remission.[49] Adalimumab (Humira)

is a fully humanized monoclonal antibody, is administered by subcutaneous injection at a dose of 40 mg (or 20 mg for children or small body mass) every 2 weeks, and can be increased to weekly if needed. Advantages over infliximab include subcutaneous administration (which achieves more stable serum concentration and allows the possibility of self-injection at home) and an improved side-effect profile as it is a fully humanized antibody with a decreased risk of allergic reactions and development of anti-drug antibodies. Etanercept, a fusion protein that blocks both TNF-α and β, is effective for psoriatic and rheumatoid arthritis, but efficacy in uveitis has not been widely established.

Potential side effects of biologics include myelosuppression, increased risk of infection (including activation of latent TB or hepatitis), liver and kidney toxicity, gonadal dysfunction, anaphylaxis, demyelinating disease, drug-induced autoimmune disease (i.e., lupus, hepatitis, psoriatic rash), and increased risk of malignancies.[50,51] Baseline CBC, liver and renal function tests, TB testing, hepatitis B and C antibody tests are required, and periodic monitoring is recommended prior to each infusion. Biologics are contraindicated in patients with a history of MS, and caution is needed before initiating therapy in pars planitis due to its association with MS.

Conclusion

Management of patients with uveitis is challenging due to the diversity of causes and clinical presentations, limited therapies approved by the US Food and Drug Administration, and a paucity of randomized controlled trials. It is important to avoid delays in diagnosis and treatment with multiple trials of regimens and combinations in order to prevent permanent vision loss. Understanding the pathogenesis may expand treatment approaches. Chronic systemic corticosteroids are associated with severe morbidity, which can be reduced by early initiation of immunomodulatory therapy and biologics. The guiding principle of treatment is a stepwise approach to achieve long-term corticosteroid-free remission. Nonetheless, each case is different and treatment should be individualized.

Declaration

All authors have disclosed no conflicts of interest.

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Review Article

Diabetic retinopathy: from pathophysiology to treatment

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Abstract

There are inter-individual variations in the severity of diabetic retinopathy despite similar glycemic control. This review discusses the pathophysiology of diabetic retinopathy that may explain these variations and different treatment options.

Key words: Diabetic retinopathy; Pathophysiology; Treatment outcome

Introduction

Diabetic retinopathy (DR) is a debilitating complication of diabetes mellitus. In Hong Kong, its prevalence in patients with type 2 diabetes is estimated to be 39%, of whom 25% have sight-threatening diabetic retinopathy.[1] According to the United Kingdom Prospective Diabetes Study (UKPDS)[2] and the Action to Correct Cardiovascular Risk in Diabetes (ACCORD) Eye Study,[3] the rate of DR is associated with glycemic control. Nonetheless, it is not uncommon to observe inter-individual variations in the severity of DR despite similar glycemic control. This review discusses the pathophysiology of DR that may explain these variations and different treatment options.

Pathophysiology

Several pathways have been implicated in the development and progression of DR, namely the increased polyol pathway, accelerated formation of advanced glycation endproducts (AGEs), activation of protein kinase C (PKC), hemodynamic changes, activation of the renin-angiotensin-aldosterone system (RAAS), inflammation and capillary occlusion and increased expression of growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1.[4]

Increased polyol pathway / aldose-reductase-sorbitol pathway

The increased polyol pathway is also known as the aldose-reductase-sorbitol pathway. In the setting of a high intracellular glucose concentration in the retina, aldose reductase, which normally functions to reduce toxic aldehydes in cells to inactive alcohols, reduces glucose to sorbitol. The latter process consumes nicotinamide adenine dinucleotide phosphate, which is an important intracellular antioxidant that plays a role in the reduction of glutathione. Decrease in glutathione reduction leads to increased cellular susceptibility to oxidative stress and damage.[5] In addition, the strongly hydrophilic sorbitol does not diffuse readily through cell membranes, thereby accumulating intracellularly and leading to possible osmotic consequences, such as damage to retinal cells or formation of cataracts.[6,7] Indeed, the association of genetic variants of the aldose reductase gene with susceptibility to DR has been demonstrated.[6] Sorbitol is slowly metabolized to fructose, which in turn is phosphorylated to fructose-3-phosphate and degraded to 3-deoxyglucosone. Both of these molecules are strong glycating agents that can result in the production of AGEs, causing further damage.[8]

Accelerated formation of advanced glycation end products

AGEs are a heterogeneous group of molecules formed through non-enzymatic reactions of reducing sugars with free amino groups of proteins, lipids and nucleic acids. AGEs are normally formed in the body at a constant but slow rate and accumulate over time. Their formation is accelerated in diabetes due to the increased availability of glucose.[9] AGEs have been implicated as a pathogenic mediator in DR. They are found in retinal vessels of patients with diabetes and their level correlates with DR severity.[10] AGEs interact with specific cell surface receptors (including receptor for AGEs [RAGE], galectin-3, CD36, and the macrophage scavenger receptor) in the course of the development of DR.[10]

Activation of Protein Kinase C

Hyperglycemia induces the activation of PKC,[11] which is associated with vascular alterations (such as increased permeability, contractility, extracellular matrix synthesis, cell growth and apoptosis, angiogenesis, leukocyte adhesion, and cytokine activation and inhibition) that cumulate in tissue damage.[12] Inhibition of PKC-β isoform by ruboxistaurin (Arxxant; Eli-Lilly) has been shown in phase III clinical trials to reduce the progression of diabetic macular edema.[13]

Hemodynamic changes

Increased blood pressure in individuals with diabetes damages the retinal capillary endothelial cells by way of increased blood flow.[14] The UKPDS reported a 2.8-fold increased risk of DR in individuals with systolic blood pressure ≥140 mm Hg, compared with those with systolic blood pressure <125 mm Hg.[15] In a UKPDS interventional trial involving the use of a β blocker or angiotensin-converting enzyme inhibitor (ACEI) and additional medications including a loop diuretic, a calcium channel blocker and a vasodilator, tight blood pressure control was associated with a 35% reduction in retinal photocoagulation, a 34% reduction in progression of retinopathy by ≥2 steps using the modified Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, and a 47% reduction in the incidence of deterioration of visual acuity by ≥3 lines using the ETDRS charts, over 7.5 years of follow up.[16]

Activation of the renin-angiotensin-aldosterone system

According to the EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes Mellitus Study, administration of lisinopril reduced progression to proliferative diabetic retinopathy by 82% in largely normotensive younger patients with diabetes.[17] As such, the renin-angiotensin-aldosterone system might have effects on DR that are independent of blood pressure. Possible mechanisms by which an ACEI acts to counter DR development and progression include beneficial hemodynamic effects, enhancement of nitric oxide resulting in a reduction of endothelial dysfunction, blockage of induction of VEGF receptors, and reduction of metalloproteinase activity improving the blood-retinal barrier.[18]

Inflammation and capillary occlusion

Hyperglycemia, oxidative stress, AGE formation, and hypertension all contribute to inflammation. This is further propagated by the inflammatory response itself, which involves the production of cytokines, adhesion molecules, VEGF signaling, enhanced RAGE expression, changes in nitric oxide regulation, and nuclear factor κB signaling.[4] Interactions between several proinflammatory factors will also lead to leukostasis, which leads to capillary-occlusion, reactive oxidative species mediated cell death and further inflammatory response.[4]

Increased expression of growth factors

The above-mentioned changes in the retina result in ischemia, which is a strong trigger for the secretion of growth factors that act to stimulate the proliferation of residual vessels. Growth factor proteins (mainly VEGF, platelet-derived growth factor, and basic fibroblast growth factor), their receptors and/or mRNA have been demonstrated histologically in pre-retinal membranes afflicted with proliferative DR.[19] Elevated vitreal levels of insulin-like growth factor 1 and VEGF have been found in individuals with neovascular activities.[19]

Treatment

Depending on the severity of DR, treatment should aim to prevent progression, promote regression and minimise loss of vision.

Intensive glycemic control (with HbA1c controlled to <6.4% vs. 7.5% in the standard therapy group at 1-year follow-up) has been shown to reduce progression of DR by 33% after 4 years of follow-up.[3] The benefit of intensive blood pressure control is less well-defined. Despite the early positive results from the UKPDS trial, later studies including the Appropriate Blood Pressure Control in Diabetes trial[20] and ACCORD Eye study[3] failed to find any significant difference in DR progression between intensive treatment (mean blood pressure, 132/78 mmHg; median systolic blood pressure, 117 mmHg) and standard treatment (mean blood pressure, 138/86 mmHg; median systolic blood pressure, 133 mmHg).

Despite a lack of evidence for the benefits of intensive blood pressure control in DR, inhibition of the RAAS by ACEI has been shown to reduce DR progression and possibly cause DR regression. In a meta-analysis of 21 randomized clinical trials with 13,823 participants, a 21% reduction in the risk of DR progression and a 43% increase in the chance of DR regression was reported in normotensive patients treated with any renin-angiotensin system inhibitor.[21] There was no benefit observed for patients who remained hypertensive despite RAAS inhibition. ACEI seemed to confer additional benefits over ARB in both reducing DR progression (OR [95% CI], 0.84 [0.75-0.94] vs. 0.92 [0.80-1.06]) and increasing DR regression (OR [95% CI], 1.50 [1.20-1.86] vs. 1.32 [107-1.61]).[21] The association of antihypertensive drugs with the risk of DR progression was lowest for ACEI, followed by ARBs, β blockers, calcium channel blockers, and placebo in rank order. The association of antihypertensive drugs with a possibility of DR regression was highest for ACEI, followed by ARBs, placebo, and calcium channel blockers in rank order. These suggest that blood pressure control is an integral part of DR management and is best achieved using ACEI, followed by the addition of β blockers and calcium channel blockers if control is suboptimal. ARBs can be used as an alternative to ACEI if necessary.

According to the ACCORD Eye Study, fenofibrate might be beneficial in reducing DR progression (adjusted OR is 0.6 at 4 years compared with placebo).[3] The putative mechanisms implicated in the mode of action of fenofibrate involve lipid and non-lipid pathways, including beneficial effects on apoptosis, oxidative stress, inflammation, blood-retinal barrier breakdown, and neuroprotection.

For severe DR, local treatment is necessary to prevent loss of vision. In addition to laser photocoagulation therapy, intravitreal anti-VEGF agents (e.g. bevacizumab and ranibizumab) are an important treatment for proliferative DR and can be considered in patients with center-involved macular edema.[22,23] Aspirin therapy for cardioprotection is not contraindicated in DR as there is no increased risk of retinal hemorrhage. For patients with proliferative DR or severe non-proliferative DR, vigorous-intensity aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment.[23]

Screening

DR is usually asymptomatic in the early stages. Early detection of DR is useful in guiding management. Screening for DR is the standard of care for those with diabetes mellitus.[23] Although retinal photography is a useful DR screening tool for non-ophthalmologists, it is not a substitute for a dilated and comprehensive eye examination, which should be performed by an ophthalmologist.[23] In the absence of retinopathy, re-examination every 2 years may be considered. If any level of DR is detected, subsequent dilated retinal examinations for patients with type 1 or type 2 diabetes should be repeated at least annually by an ophthalmologist. If retinopathy is progressing or sight-threatening, more frequent examinations are warranted. For pregnant patients, eye examination should be performed before pregnancy or in the first trimester and the patient should be monitored every trimester and/or 1 year post-partum depending on the severity of retinopathy.

Conclusion

DR is a debilitating condition with multiple pathophysiological pathways that have differential contributions to DR. Effective treatment should target all pathways by adequate glycemic and blood pressure control, reducing oxidative stress and reducing neovascularization. The intensity of glycemic and blood pressure control should be balanced against the risk of deleterious effects of hypoglycemia, hypotension or hyperkalemia (in the case of RAAS blockade).

Declaration

All authors have disclosed no conflicts of interest.

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ORIGINAL ARTICLE

A combination of pars plana vitrectomy, inverted internal limiting membrane flap technique and intraocular gas tamponade for macular hole–induced retinal detachment

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Abstract

Purpose: To evaluate the outcome of a combination of pars plana vitrectomy (PPV), inverted internal limiting membrane (ILM) flap technique and intraocular gas tamponade for macular hole–induced retinal detachment (MHRD).

Methods: Medical records of 3 men and 12 women aged 39 to 83 years who underwent PPV with inverted ILM flap technique and intraocular gas tamponade for MHRD by a single vitreoretinal surgeon were retrospectively reviewed. Outcome was evaluated with fundus examination and spectral domain optical coherence tomography. Primary outcome measures were retinal reattachment rate, macular hole closure rate and improvement in best-corrected visual acuity (BCVA). Secondary outcome measures included subjective improvement in central scotoma or metamorphopsia. The Kaplan-Meier survival curve was analyzed with non-closure of the macular hole as the end point.

Results: The retinal reattachment rate was 100%. The rate of macular hole closure was 73.3%. The mean ± SD BCVA improved from 1.73 ± 0.69 to 1.16 ± 0.51 logMAR ($p < 0.05$). All eyes had subjective improvement in scotoma and metamorphopsia. The survival rate was 86.7% at 6 months, 74.3% at 12 months, and 74.3% at 16 months. The median survival time was 18 months. No re-opening of closed macular hole or retinal re-detachment was detected. No complications such as retinal tear, retinal detachment elsewhere, persistently elevated intraocular pressure, or endophthalmitis occurred.

Conclusion: A combination of PPV, inverted ILM flap technique and intraocular gas tamponade is an effective surgical option for MHRD.

Key words: *Retinal detachment; Retinal perforations*

Introduction

Macular hole–induced retinal detachment (MHRD) can result in vision loss. The pathogenesis of macular hole formation is related to vitreo-macular tangential traction and perifoveal vitreous detachment.[1,2] Axial length elongation and posterior staphyloma formation may contribute to subsequent retinal detachment.[3,4]

Surgery for MHRD is challenging due to the complex pathogenesis. Pars plana vitrectomy (PPV) is a well-established method for the treatment of macular hole with or without retinal detachment.[5] Various surgical procedures have been proposed to improve macular hole closure and retinal reattachment rate, including removal of epiretinal membrane, removal of internal limiting membrane (ILM), endolaser photocoagulation around macular hole, intraocular gas and silicone oil tamponade.[6-10]

The inverted ILM flap technique has been shown to improve both anatomic and functional success rates for large (>400 μm) macular hole closure.[11] This study evaluated the outcome of PPV with inverted ILM flap technique and intraocular gas tamponade for MHRD.

Methods

This study was approved by the Research Ethics Committee of Kowloon West Cluster of the Hong Kong Hospital Authority. Medical records of 3 men and 12 women aged 39 to 83 (mean ± standard deviation [SD], 63.5 ± 11.9) years who underwent PPV with inverted ILM flap technique and intraocular gas tamponade for MHRD by a single vitreoretinal surgeon at the Department of Ophthalmology, Caritas Medical Centre, from 1 July 2014 to 31 December 2015 were retrospectively reviewed. Exclusion criteria included concurrent retinal pathology affecting visual acuity such as age-related macular degeneration, retinal vascular occlusions, recurrent MHRD, history of PPV, and follow-up <6 months.

A posterior vitreous detachment was first created followed by complete PPV using a 23-gauge or 25-gauge microincision. Sub-retinal fluid was drained through the macular hole. Brilliant blue G 0.025% combined with 4% polyethylene glycol stain was used to facilitate visualization of the ILM. During ILM circumferential peeling, the central one disc diameter ILM was not removed completely from the retina but was left attached to the edge of the macular hole. The ILM was then gently flipped over the macular hole from all sides using intraocular forceps until the ILM became inverted and covered the entire base of the macular hole. The remaining ILM was peeled circumferentially for up to 4 disc diameter. Fluid-gas exchange was performed with 12% octafluoropropane. Cataract surgery and intraocular lens implantation were performed simultaneously in patients with cataract. Patients were instructed to maintain a prone position for at least 2 weeks.

Spectral domain optical coherence tomography was performed at every follow-up. Primary outcome measures were retinal reattachment rate, macular hole closure rate and improvement in best-corrected visual acuity (BCVA). Secondary outcome measures included subjective improvement in central scotoma or metamorphopsia based on Amsler grid testing.

BCVA was converted to the logarithm of the minimal angle of resolution (logMAR). The BCVA of counting fingers or hand movements was assigned as the equivalent Snellen acuity of 20/2000 or 20/20000, respectively.[12] Pre- and post-operative BCVA (logMAR) was compared using the paired *t*-test. A p value of <0.05 was considered statistically significant. The Kaplan-Meier survival curve was analyzed with non-closure of the macular hole as the end point.

Results

The mean ± SD axial length of the eye was 27.9 ± 2.65 mm (**Table**); 11 of the 15 eyes (73.3%) had high myopia with an axial length >26.5 mm. The mean ± SD follow-up duration was 12.3 ± 5.0 months.

The retinal reattachment rate was 100%. The rate of macular hole closure was 73.3%, based on spectral domain optical coherence tomography (**Figure 1**). The mean ± SD BCVA improved from 1.73 ± 0.69 to 1.16 ± 0.51 logMAR ($p < 0.05$). All eyes had subjective improvement in scotoma and metamorphopsia. The survival rate was 86.7% at 6 months, 74.3% at 12 months, and 74.3% at 16 months (**Figure 2**). The median survival time was 18 months. No re-opening of closed macular hole or retinal re-detachment was detected. No complications such as retinal tear, retinal detachment elsewhere, persistently elevated intraocular pressure, or endophthalmitis occurred.

Discussion

MHRD accounts for 0.5% of all retinal detachments.[13] It occurs predominantly in highly myopic eyes and is highly prevalent in East Asia.[14-16] MHRD is considered to be caused by anteroposterior vitreous traction on the posterior pole secondary to a posterior staphyloma, tangential traction on the macular from contraction of the cortical vitreous and membranes, and the presence of atrophy of the retinal pigment epithelium and choroid.[2-4,6]

Table. Baseline characteristics.

Characteristics	Data
No. of males: females	3:12
Mean ± SD (range) age (years)	63.5 ± 11.9 (39-83)
Mean ± SD best corrected visual acuity (logMAR)	1.73 ± 0.69
Mean ± SD axial length (mm)	27.9 ± 2.65
No. of phakic: pseudophakic lens	10:5

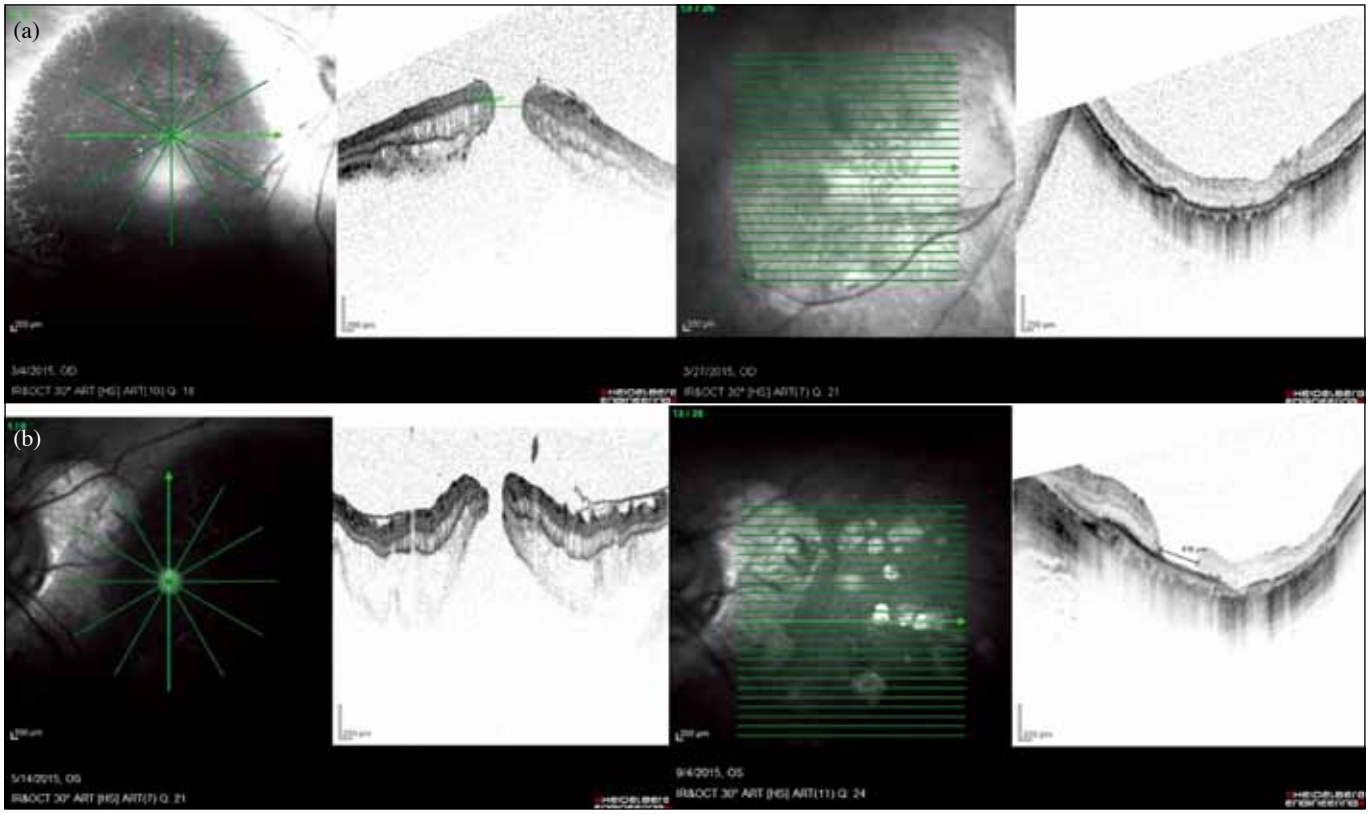

Figure 1. Pre- and post-operative optical coherence tomography of an eye with macular hole–induced retinal detachment showing (a) retinal reattachment and macula hole closure, (b) retinal reattachment but the macular hole remains flat open.

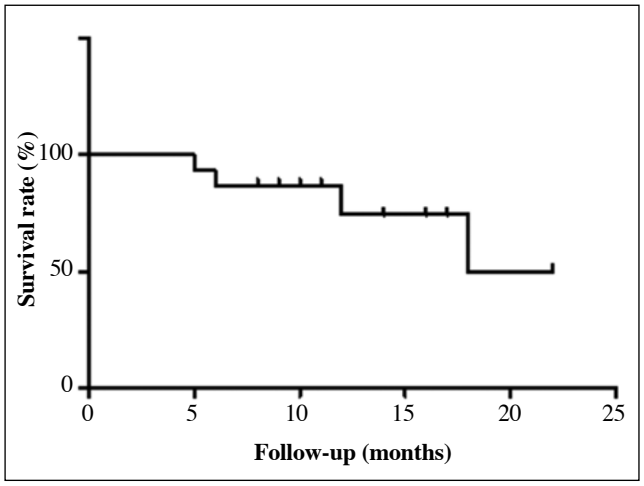

Figure 2. Kaplan-Meier survival curve showing a survival rate of 86.7% at 6 months, 74.3% at 12 months, and 74.3% at 16 months. The median survival time was 18 months. No re-opening of closed macular hole or retinal re-detachment was detected.

Surgical procedures for MHRD include macular buckle, PPV, intraocular gas tamponade, silicone oil tamponade, ILM peeling, and a combination of these approaches.[6-10] A combination of PPV, peeling of ILM, and gas tamponade is most frequently used.[6,17,18] This approach is based on the concept that perifoveal vitreous contraction and cellular components on the surface of the ILM play a role in the development of MHRD. By removing the ILM, it is expected that total removal of the overlying epiretinal membrane and cellular constituents will result in complete relief of the tangential traction.[19-21] This approach has increased the retinal reattachment rate from 85% to 91%.[7,22] Nonetheless, failure of macular hole closure remains high in MHRD, ranging from 30% to 52%.[22,23]

The inverted ILM flap technique for treating a macular hole improves both anatomic and functional outcome.[11] It was hypothesized that proliferation of glial cells is stimulated by the inverted ILM flap technique, as it produces an environment conducive to the movement of photoreceptors into direct proximity to the fovea, thereby enhancing macular hole closure.[11] Our inverted ILM flap technique differs slightly to the original technique.[11] The peripheral ILM was not trimmed; instead a larger area (up to four disc diameter) of peripheral ILM was peeled circumferentially.

Our surgical technique achieved a 100% retinal reattachment rate and a 73% macular hole closure rate, which is higher than the widely used method of complete ILM removal and gas tamponade. All patients had subjective improvement in scotoma and metamorphopsia. This could be explained

by the reattachment of 'peripheral macula', leaving only a central foveal full thickness defect. Our favorable outcome may support the hypothesis that photoreceptor repositioning at the fovea is aided by the ILM flap.[7,24] Peeling of a larger area (up to 4 disc diameter) of ILM enabled complete relief of tangential traction, and may have contributed to the improved macular hole closure rate.

Our study was limited by the small sample size and retrospective nature. A multivariate study with a larger number of patients is needed to confirm our findings.

Conclusion

PPV combined with inverted ILM flap technique and intraocular gas tamponade is an effective surgical option for MHRD. The approach achieved an excellent reattachment rate, high macular hole closure rate, and symptomatic improvement.

Declaration

All authors have disclosed no conflicts of interest.

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