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香 港 眼 科 醫 學 院

THE HONG KONG JOURNAL OF OPHTHALMOLOGY
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Purpose

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.
- Submissions pending acceptance will not be eligible for the award.
- Entries will be based on the article as a unit, but not the author. Because of this, it is possible that one single author wins both awards, given that he/she is the first author of the two best original articles published that year (but he/she has to be a trainee in this case as one award is open for trainees only).

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- Scientific merit
- Methodology
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Looking back and moving forward

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The last 2 years have seen a leap forward for the *Hong Kong Journal of Ophthalmology* (HKJO). The transformation of HKJO from a physical-only journal with distribution restricted to fellows and members, to one with both a print version and an electronic online version, with distribution beyond our local community has been a major step in making our Journal more visible to ophthalmologists globally.

With the generous support of the College of Ophthalmologists of Hong Kong, we have been able to set up a dedicated website for HKJO since May 2015. At the time of writing, our website <www.hkjo.hk> has received 2642 hits, with 28.1% from within Hong Kong and the remainder from various overseas countries (**Table**). The majority of these visitors (over 90%) are new to our website and we are starting to build a steady pool of returning readers. Alongside the launch of our own website in 2015, we have been almost simultaneously indexed by Google Scholar. Among the 2642 visits, 2150 (81.4%) were referred from searches on Google or Google Scholar. This proves the importance of having an electronic platform for HKJO, as well as being indexed by major academic search engines.

Table. Point of access of the *Hong Kong Journal of Ophthalmology* website.

Location	No. (%) of visits*
Hong Kong	742 (28.1)
United States	355 (13.4)
United Kingdom	327 (12.4)
India	151 (5.7)
Indonesia	85 (3.2)
Brazil	68 (2.6)
China (excluding Hong Kong)	53 (2.0)
Japan	46 (1.7)
Singapore	43 (1.6)
Australia	41 (1.6)
Malaysia	40 (1.5)
Canada	38 (1.4)
Italy	37 (1.4)

** Total = 2642*

Another advantage of an electronic platform is that proper statistics of reads for articles published in HKJO is made possible. For instance, the top 3 most downloaded articles of HKJO to date are: 'Update on the management of non-infectious uveitis' by Dr. Danny Ng and his colleagues[1] with 99 downloads; 'An experimental autoimmune uveoretinitis model and intraocular inflammation' by Dr. Jian Li and Dr. Wai-Kit Chu[2] with 91 downloads; and 'Safety and efficacy of dexamethasone intravitreal implant injection for macular oedema associated with retinal vein occlusion' by Dr. Angie Fong and her colleagues[3] with 81 downloads at the time of writing.

All of the above have important implications. With the indexing of HKJO in MEDLINE as the ultimate goal, there are several aspects of competence that the journal must

demonstrate. There are currently over 5600 titles indexed in the MEDLINE database, and the number is growing every year.[4] The Literature Selection Technical Review Committee (LSTRC) reviews new applicant journal titles for consideration of indexing in MEDLINE. The LSTRC meets 3 times a year and considers approximately 180 applications each time. Only approximately 12% to 15% are recommended for indexing at each meeting. Rejected journal applicants can reapply after 2 years.

The United States National Library of Medicine provides clear guidelines for indexing of a journal in MEDLINE.[5] They include, among others, a history of publishing scholarly content for a minimum of 2 years; and a scope that covers biomedical subjects. In our situation, this refers to the appropriate content with relevance to ophthalmology, the quality of the content and editorial work. The validity, importance, originality and contribution to the development of the field concerned are important key components for evaluation, as is the ability of the journal to publish an array of articles, such as reports of original research, critical reviews, and case reports, etc. The peer review process is also another important and vital element for consideration. Citations of articles published in the HKJO by other journals are also very important.

The HKJO has progressed substantially over the last 2 years. This would not have been possible without the full support of the authors, College Council, Editorial Board members and reviewers, fellows and members of the College, as well as each and every reader. In the next 2 years, together with the new Editorial Board, we hope to bring HKJO to new heights. We encourage all fellows and members to support HKJO by submitting your work to us. Even if you decide to submit your valuable work elsewhere, please consider citing works published in the HKJO, as this is also an important boost for our scientific impact. Let's work together to make HKJO an effective platform for academic exchange.

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4. *Fact Sheet MEDLINE® Journal Selection. Available from: https://www.nlm.nih.gov/pubs/factsheets/jsel.html. Accessed 4 Jul 2017.*
5. *FAQ: Journal Selection for MEDLINE® Indexing at NLM. Available from: https://www.nlm.nih.gov/pubs/factsheets/j_sel_faq.html. Accessed 4 Jul 2017.*

Review Article

What is in a posterior chamber intraocular lens? A review of the basic properties, materials and designs

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Abstract

There is a vast array of posterior chamber intraocular lenses on the market with different materials and designs. Materials used for an intraocular lens can be divided into hydrophobic and hydrophilic. Hydrophobic materials include polymethyl methacrylate, foldable hydrophobic acrylic and silicone. Hydrophilic materials include hydrophilic acrylic and collamer. The intraocular lens can be three-piece or one-piece, open-loop or plate-haptic. Different designs are also adopted to reduce posterior capsular opacification, reduce optical aberrations, filter light of unwanted or harmful wavelengths, and correct astigmatism and presbyopia. In this review, we summarize the existing literature on common materials and designs used for currently available posterior chamber intraocular lenses. It is hoped that this will facilitate surgeons in choosing an appropriate intraocular lens for their patients.

Key words: Biocompatible materials; Lens implantation, intraocular; Posterior eye segment; Prosthesis design

Introduction

With the current vast number of choices of posterior chamber intraocular lenses (IOL) on the market, it is important to understand the different properties of IOL materials and designs in order to choose a suitable IOL. From a patient's point of view, an ideal IOL should provide good visual acuity over a wide range of distances with minimal aberration and glare, and long-term stability and safety at a low cost. Surgeons will have additional considerations that include ease of handling and insertion through a small incision, intraocular biocompatibility, minimal bacterial and fungal adherence, availability of diopter range and incremental range, low posterior capsule opacification (PCO) rate, filtration of unwanted wavelengths and minimization of various optical aberrations.

Materials of intraocular lens

IOL materials are hydrophobic or hydrophilic based on the angle at which a water droplet falls on the surface of the lens (**Table 1**[1-11]). Hydrophobic materials repel water and result in a greater contact angle with water. Hydrophilic materials combine or attract water and result in a more acute contact angle with water. Amon[12] classified the biocompatibility of IOL as uveal or capsular. Uveal biocompatibility refers to the reaction of uveal tissue to the IOL, the body's natural immunologic response to a foreign object involving macrophages and foreign body giant cells. Capsular biocompatibility refers to the reaction of the residual lens epithelial cells (LEC) to the IOL. Proliferation of LEC on the anterior and posterior capsules leads to capsular opacities. Excessive proliferation is defined as low capsular biocompatibility.

Hydrophobic IOL materials include polymethyl methacrylate (PMMA), foldable hydrophobic acrylic and silicone, while hydrophilic materials include hydrophilic

Table 1. Commonly used materials for intraocular lens.[1-11]

Material	Hydrophilicity	Refractive index (RI)	Flexibility	Potential for small incision size	Capsular biocompatibility*
Polymethyl methacrylate	Inherently hydrophobic but can undergo heparin surface modification to become hydrophilic	1.49	+	+	+
Foldable hydrophobic acrylic	Hydrophobic	1.44-1.55	++	+++	++++
Hydrophilic acrylic	Hydrophilic	1.43 (newer materials developed with different RI)	+++	++++	++
Silicone	Hydrophobic	1.41-1.46	+++	++	+++
Collamer	Hydrophilic	1.45	+++	+++	+++

** Based on individual studies but no significant differences shown in meta-analysis.[1-11]*

acrylic and collamer. PMMA, foldable hydrophobic acrylic, hydrophilic acrylic and collamer are all acrylic polymers and copolymers. The mechanical properties of acrylic polymers change with temperature. At low temperatures, they are rigid and glass-like, and at high temperatures they are soft and fluid-like. This change occurs within a narrow temperature range, with the mid-point known as the 'glass transition temperature', and is important for foldable IOL. The glass transition temperature of PMMA is between 118.8°C and 113.5°C, so that at room temperature, PMMA is rigid and glass-like. The glass transition temperature of foldable hydrophobic acrylic IOL is typically below room temperature between 15.5°C and 14°C so they are foldable for insertion into the eye where it unfolds into its original shape.[13] Silicone is between –91.7°C and –119.6°C but has rubber-like characteristics at room temperature and unfolds rapidly within the eye. Hydrophilic acrylic lenses have values between 111.2°C and 95.9°C in a dehydrated state but become soft and elastic when hydrated.

Polymethyl methacrylate

PMMA is a rigid, transparent material with a refractive index of 1.49. It is inherently hydrophobic but can undergo heparin surface modification (HSM) to become hydrophilic.

Advantages of PMMA include its high uveal bio-compatibility, allowance for surface modification, good centration and resistance to tilt due to its rigidity, low cost and rare occurrence of glistenings.[13] Nonetheless, it requires a large incision due to its rigidity and is also brittle, has a higher risk of injuring the corneal endothelium, and is less tolerant to Nd:YAG laser damage during laser capsulotomy procedures.[14] It is currently used in extracapsular cataract extraction, scleral-fixated and anterior chamber IOL.

Foldable hydrophobic acrylic

Foldable hydrophobic acrylic is a series of copolymers of acrylate and methacrylate derived from rigid PMMA. The first foldable hydrophobic acrylic IOL was introduced onto the market in 1993 as the AcrySof three-piece IOL (Alcon Laboratories, Fort Worth [TX], USA). This material has become the most popular IOL material worldwide. Foldable hydrophobic acrylic IOL come in three-piece or one-piece designs, and have a refractive index of 1.44 to 1.55. Their advantages include lower PCO rate,[1-3] ease of manipulation as they are less slippery, a high refractive index that allows for a thinner optic, good resistance to Nd:YAG laser[14,15] and a relatively low risk of silicone oil condensation.[16] The minimum incision size for hydrophobic acrylic IOL is 2.2 mm, between that of silicone and hydrophilic acrylic IOL. Hydrophobic acrylic IOL can be associated with more glare and photopsia postoperatively than other materials due to their low anterior curvature and higher refractive index,[17,18] and more common occurrence of glistening.[13] 'Glistening' describes the phenomenon in which aqueous humor penetrates the IOL and water microvacuoles develop within the IOL optic giving an appearance of small bright crystals (**Figure 1**). In the majority of cases, this does not result in any significant visual alterations, although it can be associated with nighttime glare and reduced contrast sensitivity.[19] To overcome this drawback, new materials have been introduced that are pre-hydrated to equilibrium water content so that they will not accept any further water. An example is the enVista MX60 (Bausch and Lomb Incorporated, Rochester [NY], USA) [**Figure 2**].[20] There

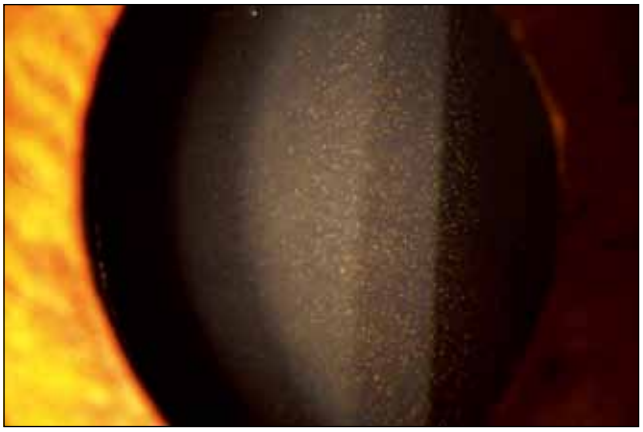

Figure 1. Slit-lamp photo of glistening of acyclic intraocular lens.

have been two case reports of significant surface deposits during implantation of a foldable hydrophobic acrylic IOL, leading to explantation.[21,22] The deposits were noted immediately after the IOL was injected into the anterior chamber and could not be entirely removed by irrigation and aspiration. Subsequent analysis of the explanted IOL suggested that the deposits might have resulted from crystallization of the ophthalmic viscoelastic device used during loading of the IOL into the cartridges. The authors proposed that the ophthalmic viscoelastic device could have dried out and precipitated on the IOL while still inside the cartridge, and the adhesive nature of hydrophobic acrylic may make removal of precipitates from the IOL surface difficult.[21]

Hydrophilic acrylic

Hydrophilic acrylic was introduced as a material for IOL in the 1980s. It comprises a mixture of hydroxyethylmethacrylate (HEMA) and hydrophilic acrylic monomer and is a heterogeneous group with highly variable water content. In hydrophilic acrylic IOL, the lower the water content, the greater the refractive index and resistance. The typical refractive index is 1.43 but newer materials have been developed that have different refractive indices, such as Akreos Adapt Advanced Optic (AO) lens (Bausch and Lomb Incorporated, Rochester [NY], USA), a copolymer of HEMA with incorporation of PMMA with a refractive index of 1.46. Two key advantages of hydrophilic acrylic IOL are their superior mechanical properties and theoretically higher uveal biocompatibility. They are softer and more compressible than hydrophobic acrylic, and hence can be implanted through a smaller incision. They are also easier to handle with a low tendency for scratch marks, and a lower risk of capsular bag damage during implantation. They are also more resistant to Nd:YAG laser[15] and have lower damage potential when touching the corneal endothelium. Hydrophilic acrylic IOL, however, have a higher PCO rate[1-3] that can be due to adherence of water molecules to the IOL surface, and lower adhesiveness to the capsule. The softer nature also makes them weaker with lower resistance to capsular bag contraction, and may not be ideal if high contraction force is anticipated, as in some eyes with pseudoexfoliation syndrome. Postoperative optic opacification of hydrophilic acrylic IOL, now rarely reported, was a significant complication leading to large-scale explantation of a hydrogel lens, Hydroview IOL (Bausch and Lomb Incorporated, Rochester [NY], USA). First used in 1999, the problems usually occurred months to years later, and appeared as fine opaque granules deposited on the surface and within the IOL optic.[22,23] It was probably caused by a deposition of calcium and phosphate salts but the exact mechanism was unknown. It was observed to be more common in patients with systemic conditions such as diabetes mellitus and hypertension, and may have been due to the associated metabolic imbalance, altered fluid dynamics of the aqueous or breakdown of the blood-aqueous barrier.[22,23] Although optic opacification is now rare with newer materials of hydrophilic acrylic IOL, there have been some case reports of opacification of Akreos Adapt AO IOL; all of which occurred in patients with diabetes.[24-26] Silicone oil adherence to hydrophilic acrylic had been reported to be lower than that for PMMA, hydrophobic acrylic and silicone IOL.[16,27] Nonetheless, calcification in hydrophilic acrylic IOL in eyes with silicone oil has been reported.[28] There has also been one case report of blue discoloration of a hydrophilic acrylic IOL (Acqua; Mediphacos, Belo Horizonte, Brazil) by intraoperative trypan blue. Acqua IOL was manufactured from hydrophilic acrylic material with a high water content (73.5%) and was implanted in a dry state. Hydration therefore depended on fluids in the capsular bag and hence could possibly absorb the dye during intraocular expansion.[29] Laboratory testing with various IOL materials showed that only hydrophilic acrylic IOL could significantly absorb commonly used capsular dyes.[30]

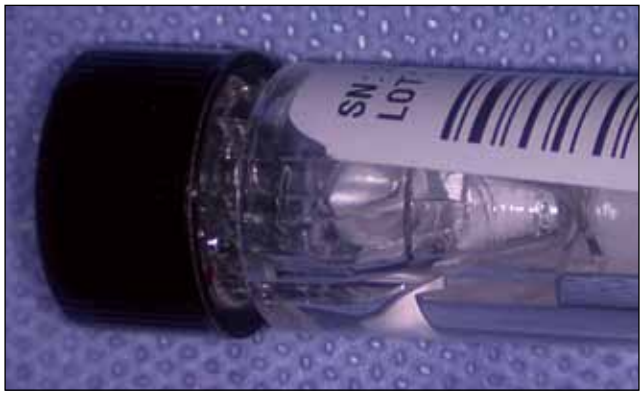

Figure 2. Prehydrated hydrophobic acrylic intraocular lens enVista MX60 (Bausch and Lomb Incorporated, Rochester [NY] USA).

Silicone

Silicone IOL are made from polymers of silicone and oxygen. They are hydrophobic with a refractive index of 1.41 to 1.46. Although silicone IOL are mechanically flexible, they are less commonly used nowadays due to their various drawbacks, including the lower refractive index and hence thicker optics and larger incision size, difficulty in manipulation because they are slippery when wet, abrupt opening inside the anterior chamber, problem of glistenings, more posterior and anterior capsular opacification compared with acrylic IOL,[1,2] low resistance to damage by Nd:YAG laser[14] and importantly, irreversible adherence of silicone droplets.[16,27,31] They are thus relatively contraindicated in patients at risk of vitreoretinal surgery such as those with diabetic retinopathy or highly myopia. They were also suspected to favor bacterial adhesion.[32] Although rare, there have been case reports of calcifications of silicone IOL in asteroid hyalosis, and tan-brown discoloration in older models.[22] Despite its drawbacks, the silicone light-adjustable lens is an exciting technology that allows spherical and even cylindrical power to be adjusted postoperatively. They contain silicone macromers that contain an ultraviolet light–activated photoinitiator. Curvature of the lens can be changed by activation of the photoreactive components by a special ultraviolet light causing polymerization in the area

of exposure so that unpolymerized macromers will diffuse into the area of treatment down a diffusion gradient. It is currently in phase 3 studies in the USA.[33]

Collamer

Collamer derives its name from the combination of collagen and polymer. It is made of a HEMA copolymer combined with a hydrophilic porcine collagen (<0.1%). It is hydrophilic and has a refractive index of 1.45. It is used exclusively in making STAAR phakic and aphakic lenses (STAAR Surgical, Monrovia [CA], USA), including the Visian Implantable Collamer lens (STAAR Surgical, Monrovia [CA], USA). Similar to hydrophilic acrylic, they have a high uveal biocompatibility[34,35] and are easy to implant due to their softness and gentle unfolding. Theoretically, the collagen in collamer attracts fibronectin that forms a layer around the IOL to promote adhesion between the collagen-containing capsule and the LEC as well as between the LEC and the IOL to prevent PCO.[35]

Material properties of intraocular lens

Capsular biocompatibility

In terms of PCO rates, the IOL material is less important than the sharp edge design. Various studies have reported higher PCO rates with hydrophilic acrylic IOL.[1,3-5] A European study of 1525 patients reported PCO and Nd:YAG capsulotomy rates to be the highest in hydrophilic acrylic, followed by PMMA, silicone and hydrophobic acrylic in decreasing order.[1] A Cochrane review of interventions for preventing PCO, however, showed no significant differences in PCO rates between different IOL optic materials.[2] The sandwich theory, which described the prevention of further epithelial ingrowth by a sealed sandwich structure formed by a monolayer of LEC bonding to both the posterior capsule and a bioactive IOL material, could theoretically account for the difference in PCO rates across different IOL materials. Foldable hydrophobic acrylic has a higher degree of bioadhesiveness, that is, the degree of adhesion of the capsule to the IOL surface, than hydrophilic acrylic, PMMA and silicone,[6-9] hence the low PCO rate. Studies that compared electron microscope images of hydrophobic and hydrophilic acrylic IOL also reported a sharper edge with hydrophobic acrylic IOL that may be related to the manufacturing process.[10,11]

Uveal biocompatibility

Hydrophilic materials are theoretically more uveal biocompatible than hydrophobic materials,[36-38] because IOL will be surrounded by aqueous humor intraocularly, and the reduced electrostatic forces and cellular adhesion may prevent attraction of inflammatory cells and adherence of fibroblasts to the surface of IOL.[39,40] A recent Cochrane review evaluating IOL in uveitic eyes, however, did not report any significant differences in uveal biocompatibility between hydrophobic and hydrophilic IOL.[41,42] Heparin coating can theoretically reduce postoperative inflammation due to the anticoagulant and anti-inflammatory effects of heparin. Nonetheless, results of whether HSM PMMA gave better outcomes in uveitic eyes compared with non-modified PMMA were conflicting, with some reporting better outcomes with HSM PMMA IOL and some reporting no statistically significant differences.[40,41,43] A randomized clinical trial comparing postoperative inflammation and capsular reaction in eyes that received heparin-coated foldable acrylic IOL and same IOL without heparin coating also failed to demonstrate any significant differences between the two groups.[44] Nevertheless, the number of reviews is limited. Studies have involved small numbers and there is insufficient evidence to show that any IOL material is superior to another for uveitic eyes that have to undergo cataract surgery.

Bacterial adherence

Hydrophilic-hydrophobic interactions may influence bacterial adhesion to IOL and may be associated with infection risk. Since postoperative endophthalmitis is rare, an extremely large sample size would be required to draw reliable conclusions. Epidemiological studies of the contribution of IOL materials have reported conflicting results. Some studies reported that polypropylene haptics and unmodified PMMA were associated with higher postoperative endophthalmitis rates.[45,46] Experimental studies reported that hydrophobic IOL such as silicone or acrylic hydrophobic IOL were more permissive to bacterial adhesion and growth than hydrophilic IOL.[32] A multicenter study by the European Society of Cataract & Refractive Surgeons also identified silicone IOL as one of the risk factors associated with postoperative endophthalmitis.[47] The results of these studies should be interpreted with caution because bacterial adhesion and endophthalmitis are complicated processes affected by many other factors such as operating technique, and ocular and systemic risk factors.

Designs of intraocular lenses

Posterior chamber IOL can have many different designs. Common designs include three-piece or one-piece, and open-loop or plate-haptic.

Three-piece intraocular lenses

Three-piece IOL consist of an optic and two open 'C-loop' haptics that are made of different materials, with the haptics inserted into two holes at the optic border. The optic can be made of PMMA, silicone or acrylic, while the haptic can be made of PMMA, polyvinylidene fluoride or polyamide. Polypropylene has previously been used for haptics but has since been abandoned because of postoperative degradation. Disadvantages of a three-piece IOL include risk of damage to the haptics when injected with an injector and hence possible need for a bigger incision than one-piece IOL, and possible brusque movements of the haptics during unfolding that may cause posterior capsular rupture. Advantages include their suitability for sulcus implantation in cases with posterior capsular rupture and good capsular fixation.

One-piece intraocular lenses

One-piece IOL are produced from a single step with optics

and haptics made of the same material. Some newer models also incorporate additional materials into the haptics, such as PMMA to the tip of the haptic in Hoya iSert 251 (HOYA Surgical Optics, Tokyo, Japan) [**Figure 3**]. One-piece IOL are more resistant to damage when implanted with injectors, and facilitate a smaller incision compared with three-piece IOL. One-piece IOL are not for sulcus placement due to the risk of iris chafing by the thick, square haptics.[45] There have been concerns about the broad haptic-optic transition on one-piece IOL leading to interrupted square edge and increased risk of PCO, but studies have not shown any differences in PCO rates between one-piece and multi-piece IOL.[46-48] Most new designs, e.g. Tecnis (Abbott Medical Optics Inc, Santa Ana [CA], USA), incorporate a 360° square edge (**Figure 4**). One-piece IOL can have open loop or plate haptics. One-piece IOL with plate haptics were used in one of the first foldable IOL (**Figure 5**). They permit a small incision and can be rotated clockwise and counterclockwise, an advantage especially for toric IOL. A major drawback is the incomplete fusion between anterior and posterior capsules along the plate-haptic axis and consequent lack of capsule bending at the optic edge theoretically allowing LEC migration and increasing the risk of PCO. Dislocation into the vitreous cavity by capsular bag contraction following posterior capsulotomy is also possible.[48] Plate-style haptics are now used in some hydrophilic IOL, collamer and silicone IOL, sometimes combined with small loop-like haptics to improve centration. Some designs use a combination of plate-style and open-loop haptics to allow adaptation to different bag sizes and reduce PCO rates. Other designs have multiple haptics to improve stability and centration in the capsular bag, such as Akreos Adapt AO IOL (Bausch and Lomb Incorporated) [**Figure 6**].

Designs to reduce posterior capsular opacification

PCO is the most frequent complication of cataract surgery, affecting 20% to 40% of patients postoperatively.[49,50] Although it can be easily treated by Nd:YAG laser capsulotomy, this will incur additional costs and the laser procedure has potential complications such as intraocular pressure spike, intraocular inflammation, IOL pitting and damage, cystoid macular edema, retinal break and retinal

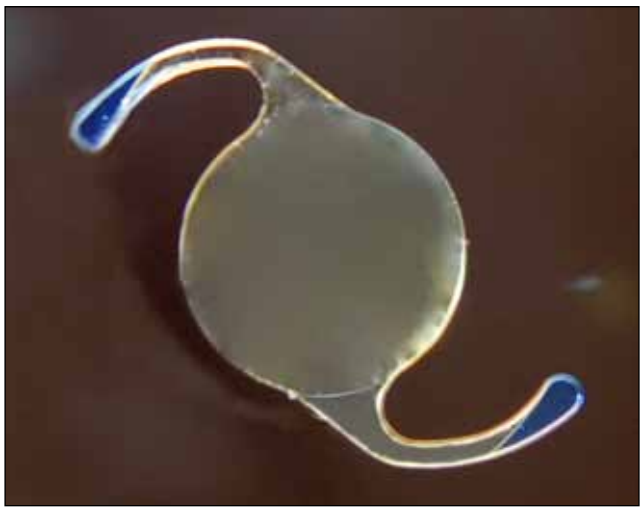

Figure 3. Incorporation of polymethyl methacrylate to the tip of the haptic in Hoya iSert 251 (HOYA Surgical Optics, Tokyo, Japan).

Figure 4. 360° square edge of Tecnis intraocular lens (Abbott Medical Optics Inc, Santa Ana [CA], USA).

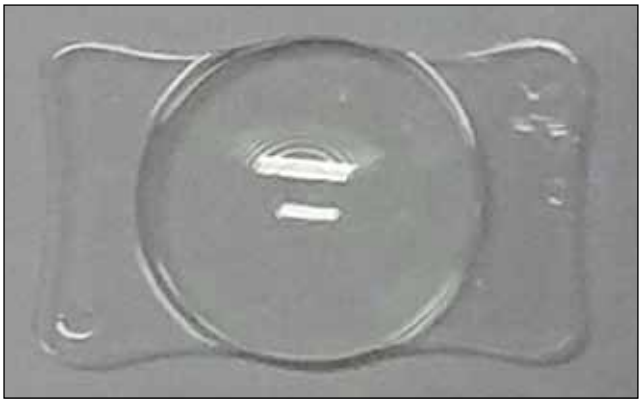

Figure 5. A multifocal intraocular lens with plate-haptic design.

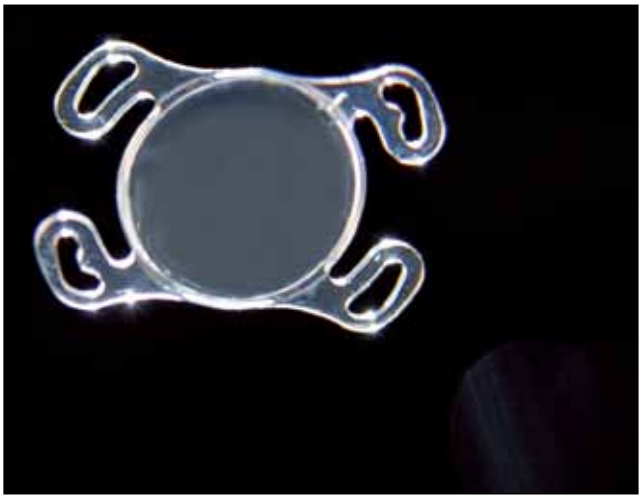

Figure 6. Four-haptic design of Akreos Adapt Advanced Optic intraocular lens (Bausch and Lomb Incorporated, Rochester [NY], USA).

Table 2. Intraocular lens designs to minimize posterior capsule opacification.	
Design	**Rationale**
Square optic edge	Prevent lens epithelial cells migration, pressure atrophy, contact inhibition
Biconvex-shaped optic	Increase contact surface with posterior capsule
Forward angulation / offset of haptics	Maintain backward position of the optic to improve contact with posterior capsule

detachment. Therefore, many efforts have been made to prevent the formation of PCO (**Table 2**). The fundamental concept is to minimize space between the posterior surface of the IOL and the posterior capsule. Measures to reduce PCO include IOL factors and surgical factors. Surgical factors are of paramount importance, such as thorough cortical clean-up, appropriately sized continuous curvilinear capsulorrhexis so that the rhexis edge overlaps the IOL optic edge entirely, in-the-bag IOL implantation and a good centration of IOL.

Optic edge

In terms of IOL design, the most important modification is the square optic edge. The square optic edge design, initially a result of the manufacturing process rather than a deliberate attempt to decrease PCO, was clearly demonstrated in several studies including a Cochrane review to significantly lower PCO rate and Nd:YAG rate compared with round-edged IOL of any material.[2] The possible mechanisms include prevention of LEC migration, pressure atrophy and contact inhibition. The advantage is reduced if the capsulorrhexis is larger than the optic as the pressure exerted by the IOL on PCO will be reduced. Nonetheless a square edge, especially when combined with a high refractive index, was reported to cause persistent 'edge-glare phenomenon'.[51-53] The optic disturbance was due to the sharp edge causing light rays that are refracted from the periphery of the IOL to be more intense on the peripheral retina, while a round edge disperses light rays over a larger surface area of the retina and hence causes less glare. Some designs to minimize the glare include a rounded anterior edge such as Sensar AR40 (Allergan Surgical, Irvine [CA], USA), and frosted edge in Tecnis ZCB00 (Abbott Medical Optics Inc, Santa Ana [CA], USA).

Optic shape

Currently, most optics of IOL are biconvex with different relationships between the anterior and posterior curvatures. The biconvex design aims to increase the contact surface with the posterior capsule to decrease the risk of PCO. The geometry of the IOL changes significantly with IOL power and some low- or minus-power lenses have a meniscus design. Optic shape directly affects the position of the principal planes of the IOL. With the change in shape of the optic as the IOL power changes from plus to minus, the principal planes shift from one side to the other and hence the A constant, which characterizes the position of the principal planes of the IOL and the effective lens position after implantation, is different for plus- or minus-power IOL.

Angulation of haptics

Some haptics have a forward angulation of 5° to 10° and this can theoretically maintain the backward position of the optic to lower the risk of iris contact and allow a greater contact area with the posterior capsule. Studies, however, have failed to demonstrate a significant reduction in IOL-posterior capsule distance or superior PCO-inhibiting effect.[54]

Reduction of aberrations

Optical aberrations are classified into different orders based on the complexity of the shape of the wavefront emerging through the pupil. With a spherical lens, the rays that pass through the periphery do not converge on the same point as those that pass through the center. With an aspheric lens, the radius of the curvature of the lens from the center to the periphery is modified so that all rays focus on a single point. Spherical aberration decreases contrast, especially at large pupils, causing problems with activities such as night driving. The shape of the cornea itself causes a positive spherical aberration. When the crystalline lens is healthy, transparent and flexible, it naturally causes negative aberration and compensates for the positive corneal spherical aberration. With aging, the spherical aberration caused by the lens becomes increasingly positive and the total aberration of the optical system increases. An aspheric IOL has a modified prolate anterior surface. They are either neutral concerning spherical aberration, which means they induce zero spherical aberration, and do not add any spherical aberration to the eye, e.g. SofPort Advanced Optics (Bausch and Lomb Incorporated, Rochester [NY], USA); or they induce negative spherical aberration that neutralizes the positive corneal spherical aberration. Designs with a highly prolate anterior surface induce a more negative spherical aberration in an attempt to negate all the corneal spherical aberration and produce a pseudophakic eye with zero spherical aberration, e.g. Tecnis ZCB00 (Abbott Medical Optics, Santa Ana [CA], USA), which indices –0.27 microns of spherical aberration. Some designs take into account that a low positive spherical aberration has been reported to be associated with 'supernormal' visual abilities,[55] and aim to leave the pseudophakic eye with a low positive spherical aberration. An example is Acrysof IQ (Alcon Laboratories, Fort Worth [TX], USA) that induces –0.20 microns of spherical aberration.

In reality, the impact of addressing asphericity is very small relative to correcting spherical error and astigmatism, hence patients are unlikely to notice any difference if they are not emmetropic. Unless the patient has a postoperative

refractive error of plano or chooses to wear spectacles to correct the residual refractive error, they are unlikely to appreciate the difference of an aspheric IOL. Studies using aspheric IOL have not shown any difference in best-corrected visual acuity, although some have shown better contrast sensitivity[56,57] and performance in nighttime driving simulation testing.[58]

Centration is another concern with some aspheric IOL. Spherical IOL do not create major problems if they decenter as they add positive spherical aberration to the optical system. IOL that are neutral concerning spherical aberration have the same power in the center and at every point out to the periphery, so if they decenter they too will not confound any existing aberrations. Nonetheless IOL that induce negative spherical aberration will induce a significant amount of coma even with low degrees of decentration or tilting. If there are concerns about IOL decentration after implantation, such as in cases of posterior capsular rupture, a standard IOL or IOL with neutral spherical aberration will be preferable.

Previous corneal surgeries may also affect the corneal spherical aberration. Patients with previous hyperopic LASIK will have a negative corneal spherical aberration while patients with previous myopic LASIK will have a more positive corneal spherical aberration. The former will benefit from a traditional spherical IOL and the latter from a negative spherical aberration IOL.

Filtering unwanted wavelengths

All IOL now filter ultraviolet light by incorporating ultraviolet light–absorbing materials because ultraviolet light is potentially toxic to the retina. Blue light–filtering IOL have also added yellow chromophore to block blue wavelength light (400-460 nm). In-vitro and animal studies have suggested that blocking short-wavelength light might be beneficial in protecting the retina.[59,60] A small study reported reduced geographical atrophy in eyes with blue light–filtering IOL,[61] but epidemiological studies regarding blue light–filtering IOL and age-related macular degeneration are still lacking. Some studies suggested a reduction in glare with blue light–filtering IOL.[62-64] With regard to visual performance of clear or blue light–filtering IOL, the majority of studies have reported similar visual acuity, photopic, scotopic and color vision performance.[65,66] The incidence of cyanopsia, where the patient notices a blue tinge to vision after surgery, has been reported to be less during the initial postoperative period in patients with blue light–filtering IOL, but no difference was reported in clear or blue light–filtering IOL at 3 months, suggesting adaptation over time.[67] A minority of patients reported subjective differences in color and contrast perception when one eye had a blue light–filtering IOL and the other eye had a clear IOL.[68] It may be safer to match the other eye if one is operated on with or without blue light filter. Studies have also shown no significant differences between clear and blue–light filtering IOL in terms of effect on circadian rhythm and sleep-wake cycle,[69,70] effect on optical coherence tomography imaging[71] and visual field testing,[72] or intraoperative impediment and postoperative outcomes in combined cataract and vitreoretinal surgery.[73]

Correcting astigmatism

Toric IOL effectively neutralize pre-existing corneal astigmatism in cataract patients at the time of surgery. Systematic reviews have shown promising clinical outcomes in toric IOL implantation, in particular superior uncorrected distance visual acuity, greater spectacle independence and lower amounts of residual astigmatism compared with non-toric IOL.[74,75] Currently, a wide range of models of toric IOL is commercially available, for example, AcrySof IQ Toric and AcrySof IQ ReSTOR multifocal toric (Alcon Laboratories, Fort Worth [TX], USA), Tecnis Toric (Abbott Medical Optics, Inc, Santa Ana [CA], USA), Trulign Toric (Bausch and Lomb Incorporated, Rochester [NY], USA), Staar Toric (Staar Surgical, Monrovia [CA], USA), etc. Toric IOL are made of hydrophobic acrylic, hydrophilic acrylic, silicone or PMMA biomaterials.[76]

Accurate axis placement of the toric IOL is key to achieving good refractive outcome as 3.3% of toric correction is lost for every degree off the desired axis.[77] Being 30° off axis will result in complete loss of astigmatic correction. Toric IOL have a marking on the optic to guide alignment with the steep axis of the cornea, and should be marked with the patient seated as the eye may undergo cyclotorsion when the patient assumes a supine position.[78] Innovative intraoperative wavefront aberrometry, iris fingerprinting, limbal registration and other surgical guidance systems can improve the accuracy of alignment. Rotational stability, especially when the capsular bag contracts and the anterior and posterior capsular surfaces fuse, is also crucial for toric IOL efficiency. Toric IOL design and materials have been shown to play a role. A randomized controlled trial demonstrated that one-piece acrylic toric IOL had better rotational stability than a plate-haptic silicone toric IOL.[79]

Correcting presbyopia

Accommodative function of the natural lens is lost after cataract surgery and as a consequence, spectacles will be required for near vision if standard monofocal IOL are used. Presbyopia-correcting IOL have been developed to overcome this loss of accommodation. Multifocal IOL and accommodating IOL are in this armamentarium.

Multifocal intraocular lenses

Multifocal IOL are designed to overcome a lack of accommodation by dividing the incoming light onto two or more focal points for distance, near or intermediate vision. The two broad categories of multifocal IOL are diffractive and refractive lenses. Diffractive multifocal IOL utilize diffractive zones across the lens surface to create different focal points.[80] They can be further enhanced via apodization to allow for progressive variation across the zones,[81] in order to improve efficiency and optimize quality of vision achieved. Refractive multifocal IOL work by incorporating different powers into circular refractive zones.[80] AcrySof

ReSTOR IOL (Alcon Laboratories, Fort Worth [TX], USA) has a central diffractive portion, while ReZoom (Abbott Medical Optics, Inc, Santa Ana [CA], USA) and Tecnis Symfony multifocal lenses (Abbott Medical Optics, Inc, Santa Ana [CA], USA) are examples of multifocal IOL based on refractive principles.

A meta-analysis of peer-reviewed publications demonstrated the effectiveness of multifocal IOL, with a mean spectacle independence of 80.1%.[82] Nonetheless visual complaints after surgery are more common in multifocal than monofocal IOL.[83] These visual problems include reduced contrast sensitivity and the photic phenomenon of halo and glare, resulting in suboptimal visual quality. With neuroadaptation, the effect of optical aberrations may lessen after a period of adjustment,[84] but the neural adaptability to multifocality varies greatly among individuals.

Accommodating intraocular lenses

To overcome the lack of accommodation in pseudophakic patients and to avoid optical side-effects of multifocal IOL, accommodating IOL have been developed. These are dynamic devices designed to effect a change in optical power in response to contraction of ciliary muscles and axial movement of the optic, thereby restituting the accommodative function of the eye.[85] There are two main types of accommodating IOL: single optic and dual optic.

The single-optic lens was developed first and several models are available, such as Crystalens (Bausch and Lomb Incorporated, Rochester [NY], USA), 1CU (HumanOptics AG, Erlange, Germany), Tetraflex (Lenstec Inc, Florida, USA) and Tek-Clear (Tekia, California, USA). Nonetheless the limitation of single-optic accommodating IOL stems from the small amplitude of excursion[86] that translates into insufficient accommodative power generation to yield adequate and consistent near vision. The accommodative response in eyes implanted with accommodative IOL has been reported to be lower than 0.4D using laser ray tracing aberrometry.[87] Dual-optic accommodating IOL are different in that there are two coaxial optics. They comprise a high-plus power anterior optic coupled to a compensatory minus posterior optic by a spring system. This maximizes the production of accommodative power by design.[88] Synchrony dual-optic accommodating IOL (Visiogen, Inc, Irvine [CA], USA) and Sarfarazi Elliptical Accommodating IOL (Bausch and Lomb, Rochester [NY], USA) are examples.

Accommodating IOL appear to be an up-and-coming alternative to monofocal or multifocal IOL in achieving spectacle independence, but at present they are still in the nascent stage of development. More large-scale studies of their efficacy and safety are necessary to support a transformation of practice.

Conclusion

With a sound knowledge of the various properties of an IOL, surgeons can discuss with patients the different options, choose the best IOL for their patients, especially in special conditions such as chronic uveitis, and optimize the postoperative visual outcome.

Declaration

All authors have disclosed no conflicts of interest.

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Review Article

Demyelinating and inflammatory optic neuropathies: an update

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Abstract

Optic neuritis is one of the leading causes of vision loss in young to middle-age populations worldwide. Although it has been documented to account for the initial presentation in up to one-fifth of multiple sclerosis patients among Caucasian populations, the clinical course and etiologies of the condition are less well-defined in Asians. Chinese patients have lower conversion rates to multiple sclerosis as well as a higher incidence of neuromyelitis optica–associated optic neuritis and optic perineuritis, demonstrating considerable ethnic differences. The need to better characterize the differentiating features between three clinically similar entities: multiple sclerosis–associated optic neuritis, neuromyelitis optica–associated optic neuritis and optic perineuritis, is warranted to facilitate proper management.

Key words: Multiple sclerosis; Neuromyelitis optica; Optic neuritis

Introduction

Optic neuritis (ON) is a disorder of the optic nerve that classically presents with the triad of vision loss, periocular pain and dyschromatopsia.[1,2] It is conventionally classified into typical and atypical forms, whereby typical ON is taken to be demyelinating cases associated with multiple sclerosis (MS) and atypical ON with non-MS immune-mediated etiologies including neuromyelitis optica (NMO-ON) and systemic disorders such as connective tissue and granulomatous conditions.[3] For the purpose of this review, we will focus on MS-ON and NMO-ON because of their clinical importance and demand for early differentiation given their dissimilar management modalities and prognoses. Meanwhile, optic perineuritis (OPN), a form of idiopathic orbital inflammatory disease (IOID) that targets the optic nerve sheath, has in recent years been found to share deceptively similar presentations to ON, with both conditions bringing about acute monocular vision loss, pain on eye movement and a normal or swollen optic disc. OPN therefore represents a key differential diagnosis in cases of suspected ON, and will for this reason also be included in our discussion.[4] This article will review our current understanding of the three disease entities, MS-ON, NMO-ON and OPN; delineate features crucial for their differentiation in terms of presentation, investigative findings,[5,6] treatment and prognosis; and propose recommendations for the most appropriate clinical approach.

Idiopathic demyelinating optic neuritis / multiple sclerosis–associated optic neuritis

A patient who develops typical idiopathic demyelinating optic neuritis (IDON) is usually an otherwise healthy young adult, commonly 20 to 45 years of age and 3 times more likely to be a woman than a man. It is also more reliably associated with MS when found at higher latitudes and in Caucasians.

IDON usually presents with acute painful monocular vision loss accompanied by field loss, dyschromatopsia and periocular pain.[7] The classic pattern is loss of vision progressing over a span of hours to 10 days, with a spectrum

of severity ranging from mild to no light perception and normally reaching its nadir within 2 weeks. Any form of visual field defect is possible in IDON, although the 15-year follow-up report from the Optic Neuritis Treatment Trial (ONTT) reported diffuse and central field losses to be more commonly detected at the initial visit, and partial arcuate, paracentral and arcuate type losses at subsequent follow-ups.[8] Complete or near-complete recovery of visual acuity and field loss is common, and in fact any progressive worsening of vision lasting over 2 weeks, or a lack of recovery beyond 8 weeks after symptom onset should prompt investigations for an alternative diagnosis.[9] Dyschromatopsia, or impaired color vision, occurs early on in the course of IDON and is often out of proportion to the degree of visual acuity deficit. The type of color defect, however, does not appear to correlate with severity of visual impairment. The ONTT described mostly mixed color defects, with blue-yellow defects prevailing in the acute phase and red-green defects more common at 6 months,[10] while other studies largely reported red-green and blue-yellow defects with no particular predominance.[11] Up to 30% of IDON patients experience phosphenes[12] that are bright, fleeting flashes of light with eye movement. Periocular pain and retro-orbital pain occur in more than 90% of cases[13]; it can precede or coincide with the onset of vision impairment and is aggravated by eye movement but is usually non-severe and often resolves within days. Additional clinical findings may include the MS-specific but semi-sensitive Uhthoff's phenomenon[14] and Pulfrich phenomenon, being rather non-specific for MS-ON.[15]

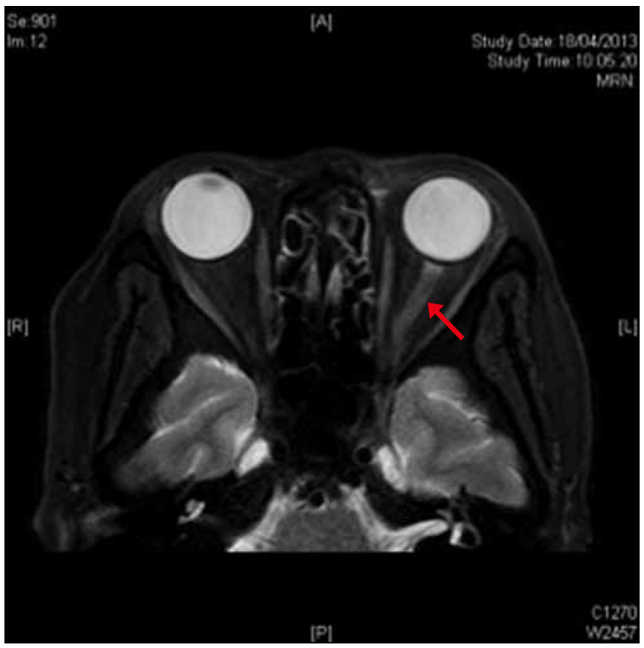

Figure 1. A 25-year-old female with first episode of left idiopathic demyelinating optic neuritis: the magnetic resonance imaging scan shows T2 homogeneous hyperintensity over the whole course of optic nerve (arrow).

The diagnosis of MS-ON is a clinical one. The ONTT supports that for a patient who presents with typical ON, laboratory studies and radiological imaging of diagnostic intent are unnecessary.[16] That said, findings from investigations, if performed, can aid the differentiation between MS-ON, NMO-ON and OPN, as well as prognosticate the future risk of developing clinically definite multiple sclerosis (CDMS). In MS-ON, magnetic resonance imaging (MRI) of the optic nerve with gadolinium pinpoints the culprit optic nerve lesion in 95% of patients (**Figure 1**)[17]; contrast enhancement of the optic nerve is a sensitive (94%) finding in acute ON,[18] but no published data have yet elucidated its role in MS-ON/NMO-ON distinction. Brain MRI with gadolinium may reveal the characteristic spatial and temporal dissemination of lesions required for a diagnosis of MS set forth by the 2010 McDonald MRI criteria (**Table 1**).[19] The presence of demyelinating white matter lesions in brain MRI scans, 3 mm or larger in diameter, ovoid in shape, located in periventricular areas of the white matter and radiating toward the ventricular spaces, has been identified as the single most predictive factor for conversion to CDMS.[20] In the ONTT, 25% of patients with no MRI lesions at presentation still went on to develop MS; 50% of those with one or more MRI lesions developed MS within 5 years[21] and 72% within 15 years.[22] Optical coherence tomography may be employed to visualize the retinal nerve fiber layer (RNFL); the thickness of which increases in the initial period of optic nerve swelling but subsequently decreases secondary to axonal loss. Such thinning, albeit present, should be to a lesser extent than that in NMO-ON eyes; results of one study propounded that any RNFL thickness loss greater than 15 μm in patients without established symptoms or signs of MS should impel investigations for underlying NMO-ON.[23] Finally, a lumbar puncture performed in MS-ON will demonstrate raised cerebrospinal fluid (CSF) oligoclonal bands alongside mild pleocytosis. A high CSF pleocytosis is, however, a very rare occurrence in MS-ON and heightens the likelihood of an alternative, atypical etiology.[24]

Table 1. 2010 McDonald magnetic resonance imaging (MRI) criteria for multiple sclerosis.[19]

Diagnosis of multiple sclerosis requires elimination of other diagnoses and demonstration of dissemination of lesions in space and time	
Dissemination in space	At least one lesion visible on T2-weighted scan in at least 2 of 4 locations: juxtacortical, periventricular, infratentorial and spinal cord
Dissemination in time	(1) A new T2 lesion or gadolinium-enhancing lesion visible on a follow-up MRI scan when compared with a previous scan (which is taken as the baseline scan) obtained at any time following the onset of symptoms; or (2) An MRI scan showing simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time

The clinical course of IDON follows a reasonably predictable trajectory. Spontaneous improvement in visual function is observed in more than 80% patients within 2 to 3 weeks even in the absence of treatment,[25] followed by stabilization or sustained improvement over a period of up to 1 year. Nonetheless, despite the relatively rapid and apparently complete recovery (median visual acuity at 6 months of 20/16,[26] and >85% patients scoring 20/25 or better at 5 years[27]), significant persistent complaints are not rare. Treatment options for MS-ON are manifold; acute treatment can take the form of corticosteroids, plasmapheresis or intravenous immunoglobulins, and long-term treatment can take the form of the disease-modifying drugs beta-interferon and glatiramer acetate. To date, only corticosteroid therapy has consistently produced beneficial therapeutic effects in the acute management of MS-ON, whereby high-dose intravenous corticosteroids followed by an oral taper accelerates initial visual recovery. Multiple studies, however, have concurred that corticosteroids have no bearing on the eventual vision outcome when compared with placebo, among which the ONTT offers the most reliable information regarding the long-term outcome.[28] Intravenous methylprednisolone delayed the onset of CDMS at 2 years, but this difference dwindled over time and no statistically significant difference in visual function was discernable between the groups in the long run.[22] Based on the findings of the ONTT, treatment with oral corticosteroids in conventional doses alone is contraindicated due to the proven increased risk of a second episode.[29] Intravenous corticosteroid therapy, meanwhile, is recommended for typical ON patients in the presence of 3 or more MRI signal abnormalities, as well as for patients in whom there exists a need for prompt resolution of visual deficits, including monocular patients, bilateral disease involvement, patients with employment demands and according to individual patient preference, with the rationale of reducing 2-year risk of MS development.[30]

Regarding long-term management, a number of placebo-controlled trials have demonstrated the efficacy of disease-modifying agents in delaying subsequent relapse and conversion to CDMS in MS-ON patients positive for MRI demyelinating lesions[31-33] persisting for 5 years in one particular follow-up study.[34] The latest guidelines from the Association of British Neurologists recommend that disease-modifying drugs be considered for patients who present with clinically isolated syndrome and demyelination on MRI, but precise clinical protocols remain locality specific.[35] The CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study)[36] was a randomized, double-blind trial involving 383 patients with an initial, acute monosymptomatic demyelinating event—either unilateral ON, incomplete transverse myelitis or brainstem/cerebellar lesion, and at least 2 silent T2 lesions on MRI brain—who were given either weekly intramuscular interferon-β1a or placebo. Acutely the treatment group exhibited statistically significant improvements in all MRI parameters, and 10-year follow-up demonstrated that patients treated as soon after their first episode as possible had a significantly lower chance of having a second episode than those who received delayed (beyond 30 months) treatment, corroborating the benefits of prompt initiation of interferon-β1a. This was confirmed by the PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Trial,[37] which established that interferon treatment in dosages of 22 μg and 44 μg yielded lower relapse rates than control, as well as the BENEFIT (Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment) study[38] that described a 50% reduction in risk of MS at 2 years in patients treated with interferon β-1a. Nevertheless, immunomodulatory treatment is not routinely recommended for all patients with MS-ON for the following reasons: (1) low prevalence of MS in Asian countries; (2) lack of consensus on ideal treatment endpoint; (3) efficacy of disease-modifying drugs in preventing long-term disability is yet unproven and (4) MS, as opposed to NMO, tends to follow a favorable disease course. On this basis, the current recommendation is for patients with a normal initial MRI brain to be followed up with surveillance MRI at least annually, to look for the development of any new white matter lesions. Patients with one or more MRI lesions, on the other hand, should be given the option of immunomodulatory treatment and closely followed up with serial MRI scans.[39]

Inflammatory optic neuropathy

Neuromyelitis optica–associated optic neuritis

NMO is an autoimmune inflammatory disorder of the central nervous system characterized by recurrent bouts of ON and transverse myelitis, features also found in MS. NMO has therefore for decades been considered a variant of MS rather than an independent disease entity. This notion, however, evolved upon the discovery in 2005 of serum antibodies against the water channel protein aquaporin-4 (AQP4) in NMO patients,[40] and demonstrated fundamentally distinct immunopathogenesis between NMO and MS. Traditionally, NMO was thought to be a monophasic disorder characterized by simultaneous onset of bilateral ON and transverse myelitis, but in 2006 the incorporation of AQP4—immunoglobulin G (IgG) serology into the diagnostic criteria permitted more liberal clinical requirements, allowing unilateral ON or asymptomatic MRI brain lesions to be counted. Nevertheless there exist patients with overlapping features of both NMO and MS, who test negative for serum AQP4 antibodies, and in whom a definitive diagnosis may not be confidently made. In some instances the diagnosis of NMO is made after deterioration following disease-modifying treatments set out to target MS. A year later in 2007, the term neuromyelitis optica spectrum disorder (NMOSD) was coined, having established that the diagnosis of NMOSD should not be based solely upon the presence or absence of AQP4-Ab. The International Panel for NMO Diagnosis published a set of diagnostic guidelines for NMOSD in 2015, stratified according to AQP4-IgG status (**Table 2**).[41] Due to the dissimilar first-line management options and prognoses of NMO-ON and MS-ON, it is critical that guidelines be developed to better differentiate between the two.

Table 2. International Panel for NMO Diagnosis—2015 diagnostic criteria for NMOSD.[41]

Disorder	Diagnostic criteria
NMOSD with AQP4-IgG	(1) At least 1 core clinical characteristic* (2) Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) (3) Exclusion of alternative diagnoses
NMOSD without AQP4-IgG or AQP4-IgG status unknown	(1) At least 2 core clinical characteristics* occurring as a result of ≥1 clinical attacks and meeting all of the following requirements: (a) At least 1 must be optic neuritis, active myelitis with LETM, or area postrema syndrome (b) Dissemination in space (2 or more core clinical characteristics) (c) Fulfillment of additional MRI requirements†, as applicable (2) Negative test for AQP4-IgG using best available detection method, or testing unavailable (3) Exclusion of alternative diagnoses

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis; MRI = magnetic resonance imaging; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder.

* *Core clinical characteristics include:*
- *(1) Optic neuritis*
- *(2) Acute myelitis*
- *(3) Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting*
- *(4) Acute brainstem syndrome*
- *(5) Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions*
- *(6) Symptomatic cerebral syndrome with NMOSD-typical brain lesions*

† *Additional MRI requirements for NMOSD without AQP4-IgG or AQP4-IgG status unknown:*
- *(1) Acute optic neuritis: requires brain MRI showing (a) normal findings or only non-specific white matter lesions, or (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over 1/2 optic nerve length or involving optic chiasm*
- *(2) Acute myelitis: requires associated intramedullary MRI lesion extending ≥3 contiguous segments (LETM) or ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis*
- *(3) Area postrema syndrome: requires associated dorsal medulla/area postrema lesions*
- *(4) Acute brainstem syndrome: requires associated periependymal brainstem lesions*

The epidemiologic and demographic differences between NMO and MS may prove helpful in the initial prioritization of the two conditions. While MS displays a prominent geographic distribution and prevails in the white population, NMO in comparison appears to have a more worldwide occurrence, with 20% to 50% of NMO patients quoted to be of non-white ethnicity in the UK and US studies.[42] The age of onset of symptoms is also different. NMO patients are on average 10 years older than MS patients at initial presentation, with a mean age of onset at 40 years and 30 years for NMO and MS, respectively. Worthy of note is the fact that while late-onset MS after the age of 50 years is not unseen, a very late onset beyond the age of 70 years is exceptionally uncommon.[43] This is in stark contrast to NMO, for which the UK studies have reported over one-fifth of Caucasian patients have an age of onset of over 60 years.[44] A very late age of onset may thus favor a diagnosis of NMO.

Approximately 50% of NMO patients initially present with isolated ON, among whom 20% have bilateral involvement.[45] Isolated simultaneous bilateral ON in particular is a syndrome classically associated with NMO-ON and only rarely encountered in MS-ON. Moreover, as opposed to MS-ON, which tends to yield a good prognosis, NMO-ON usually causes more profound and persistent vision loss. During an acute attack, 80% of NMO-ON patients experience a visual acuity of less than 20/200, with a corresponding 36% in MS-ON. Approximately 60% of NMO-ON patients experience unilateral or bilateral blindness at a median of 7.7 years following disease onset, in contrast to only 4% of MS-ON patients at 15-year follow-up.[46,47] The pattern of visual field defects also provides valuable diagnostic information; altitudinal field deficits, if present, corroborate a diagnosis of NMO-ON as it is encountered only in NMO-ON (in >10% patients), not MS-ON (**Figure 2**).[48]

Apart from clinical features, NMO-ON may be distinguished from MS-ON by imaging and investigative findings. In pediatric NMO-ON patients, the MRI findings are quintessentially long-segment, occasionally bilateral, optic nerve enhancement with extension into the optic chiasm,[49] whereas in adults the lesions are usually more extensive with posterior portions of the optic nerve more commonly involved in NMO-ON than in MS-ON.[50] Optical coherence tomography of eyes affected by NMO-ON exhibits more marked peripapillary RNFL loss than in MS-ON[23]; in the first reported Chinese case of NMOSD associated with ocular myasthenia gravis, the patient had an average RNFL thickness of only 33 μm and 39 μm over the right and left eye, respectively, much thinner than the mean thickness of those with idiopathic ON at 3 months post attack (103.9 ± 6.0 μm)[51]; and while RNFL thinning in MS-ON shows a definite predilection for the temporal quadrant, more widespread atrophy involving the superior and inferior quadrants is often seen in NMO-ON.[52] In terms of CSF findings, patients with NMO often have more prominent pleocytosis[53] and possibly neutrophils and eosinophils, in contrast to the presence of lymphocytes and macrophages in MS patients.[46] Oligoclonal bands, present in up to 95% of patients with MS, are

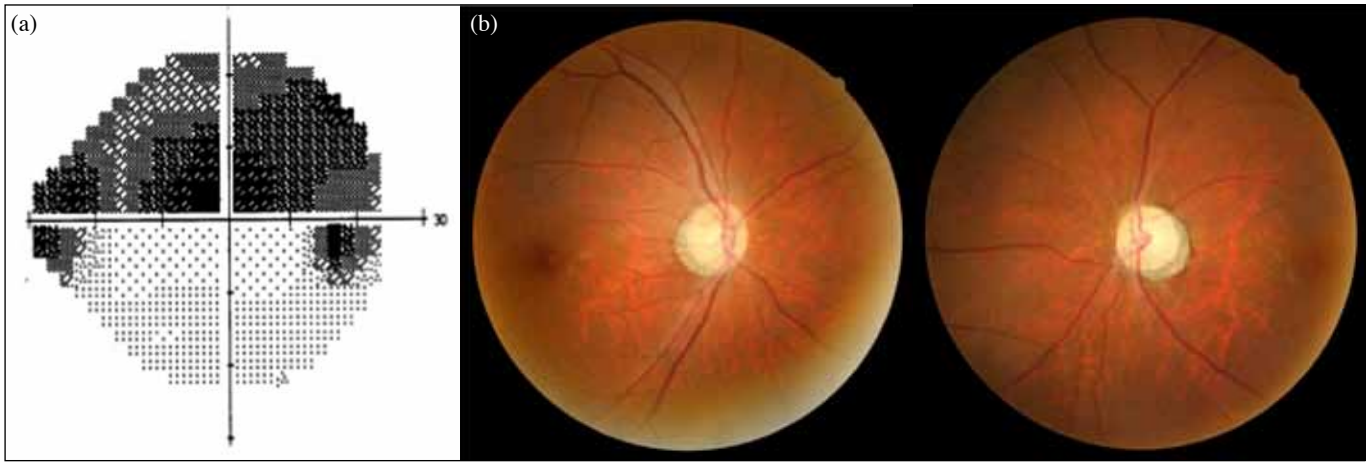

Figure 2. A 33-year-old female initially presented with reduced visual acuity (VA) of 6/12 in the right eye. (a) Superior altitudinal visual field loss and pain on eye movement. Her VA returned to 1.0 but had an incomplete visual field recovery after Optic Neuritis Treatment Trial (ONTT) regimen. Later on she had two further episodes of left severe visual loss, with nadir VA down to 0.4 and finger count of 1 m. Unfortunately she only received further ONTT regimen without long-term maintenance. Finally, she ended up with VA of 1.0 in the right eye and no light perception in the left eye. (b) There is bilateral optic disc pallor and severe nerve fiber layer loss, worse in the left eye. A subsequent aquaporin-4 antibody testing turned out to be positive.

detected in 10% to 25% of patients with NMO.[54]

Finally, knowledge of the pathogenesis of NMO has prompted the measurement of astrocyte-specific biomarkers, including AQP4 antibodies and glial fibrillary acidic protein (GFAP). A 2010 study demonstrated much higher levels of GFAP during an acute relapse of NMO than would be present in a case of MS, with a mean of 2477 ng/mL and 0.8 ng/mL, respectively.[55] Furthermore, pro-inflammatory cytokines such as interleukin 6, involved downstream of astrocyte destruction in the pathogenesis of NMO, may also be employed as potential biomarkers. In several preliminary studies increased interleukin 6 levels were detected in NMO but not in MS patients.[56] Antibodies to AQP4 in particular are a sensitive and highly specific serum marker of NMO that can aid the differential diagnosis of NMO-ON and MS-ON. To date, a multitude of assays exist for the detection of AQP4 antibodies and, depending on the substrate used, these may be classified into cell-based assays, tissue-based assays or protein-based assays. A comparison of their respective working mechanisms, advantages and limitations is made in **Table 3**.[57] The International Panel for NMO Diagnosis recommends the use of cell-based serum assays because of their superior accuracy, but these are not yet widely available.

The management of NMO-ON is two-tiered. First, during initial and subsequent acute attacks, patients should be treated with high-dose intravenous methylprednisolone (1 g daily for 3-5 consecutive days) because of the implications for prognosis if treatment is delayed. For patients in whom symptoms are severe or refractory to glucocorticoids, plasmapheresis is the recommended adjunct. Second, as soon as the diagnosis of NMO-ON is established, attack prevention should be viewed as an essential component of patient management, taking the form of long-term systemic immunosuppression via agents such as azathioprine, mycophenolate mofetil, rituximab and oral glucocorticoids. To date there is no consensus on the optimal duration of immunosuppressive treatment, but the prevailing practice is for AQP4-seropositive patients to receive immunosuppression for a minimum of 5 years.[58] The Expanded Disability Status Scale, annualized relapse rate and visual outcome scores may be employed where necessary to determine treatment efficacy with immunosuppressants. According to one study, efficacy of azathioprine was associated with an increased mean corpuscular volume by at least 5 points from baseline, but further studies are needed to delineate the correlation between rise in mean corpuscular volume and efficacy of azathioprine.[59] As previously put forth, NMO-ON and MS-ON have heterogeneous pathogeneses and treatment responses. This is particularly relevant in the context where exacerbation of underlying, misdiagnosed NMO-ON occurs as a result of treatment with MS-modifying drugs such as interferon beta,[60] with consequent catastrophic outcomes with the development of extensive brain lesions. The differential diagnosis between the two is therefore paramount. The above-mentioned NMO/MS discriminators — in terms of demographics, clinical features, laboratory and imaging findings — may prove useful in the assessment of the patient who presents with equivocal symptoms.

Optic perineuritis

OPN also known as perioptic neuritis, is a rare form of an IOID that affects dural sheath of optic nerve and is distinct from demyelinating ON. Although most cases are isolated

Table 3. Comparison of assay methods for detection of AQP4 antibodies.[57]

	Cell-based assays	Tissue-based assays	Protein-based assays
Mechanism	Cell lines such as human embryonic kidney cells transfected with the target antigen are allowed to react with patient serum. Mock-transfected or non-transfected cells from the same cell line are employed as control. Binding of patient serum to the test but not control set indicates presence of antibodies of interest	Tissue sections are prepared from tissues known to express the target antigen and incubated with patient serum. A secondary antibody to human IgG, either labeled with a fluorescent (IHC-F) or non-fluorescent (IHC-C) dye, is applied and a diagnosis made based on antibody- and tissue-specific binding patterns	Recombinant AQP4 protein is incubated with patient serum
Subtype	(a) IHC-F (b) Flow cytometry (FACS) (c) Cell-ELISA	(a) IHC-F (b) IHC-C	(a) RIPA (b) FIPA (c) WB (d) ELISA
Advantage	Higher sensitivity and specificity than tissue-based assays	(a) Widely available (b) Only method that allows the detection of coexisting paraneoplastic or connective tissue-disease associated antibodies, especially relevant in NMO-IgG/AQP4-Ab–negative patients	(a) ELISA provides quantitative data, useful for long-term monitoring of antibody levels (b) Good for large sample sizes (c) WB allows detection of some paraneoplastic antibodies (d) Higher sensitivity in ELISA than tissue-based assays
Limitation	(a) The use of non-stably transfected cell lines implies a need for them to be maintained over time and transfected just prior to testing, hence limited reproducibility and availability (b) Semi-quantitative and observer-dependent (c) Rheumatic, paraneoplastic and new autoantibody reactivities cannot be detected	(a) Results are observer-dependent and subjective, and at best semi-quantitative (b) Lower sensitivity than protein-based assays (c) IHC-F is labor-intensive and time-consuming	(a) Lower sensitivity than cell-based assays (b) High false-positive rate due to patient antibodies binding to fluorophores (in FIPA) (c) FIPA is labor-intensive and time-consuming (d) Limited availability

Abbreviations: AQP4 = aquaporin-4; ELISA = enzyme-linked immunosorbent assay; FACS = fluorescence-activated cell sorting; FIPA = fluoroimmunoprecipitation assay; IgG = immunoglobulin G; IHC-C = conventional immunohistochemistry; IHC-F = fluoroimmunohistochemistry; ; NMO = neuromyelitis optica; RIPA = radioimmunoprecipitation assay; WB = western blotting.

and idiopathic, OPN occasionally occurs as a manifestation of a specific infectious or inflammatory disorder, such as Wegener's granulomatosis, giant cell arteritis,[61] Crohn's disease,[62] acute phase of secondary syphilis[63] as well as a manifestation of neurosyphilis[64] and with pre–B-cell lymphocytic leukemia.[65]

OPN has been known to present in 2 forms, first as an exudative form with a focal non-suppurative pachymeningitis and second as a purulent form with leptomeningitis and involvement of the subarachnoid space around the optic nerve. These occur as a result of varied processes such as granulomatous inflammation of the sheath,[66] and necrobiotic degeneration of collagen in the dura or perivascular lymphocytic infiltration of small optic nerve vessels (vasculitis). Regardless of the initiating mechanism, non-specific fibrotic thickening of the dural nerve sheath ensues[64] and leads to secondary demyelination and/or infarction of the optic nerve as a result of compression by the thickened nerve sheath. This has led to the belief that OPN represents a response to a spectrum of disorders.[67] ON, on the other hand, consists of myelin degeneration and axonal death secondary to type IV hypersensitivity reaction.

OPN is difficult to differentiate from ON clinically as both conditions present with similar symptoms and signs. In ON, vision loss usually occurs in younger females and is central and often self-limiting. In OPN, vision loss tends to occur in older patients (age >50 years) and is peripheral or arcuate. It is therefore important to consider the possibility of OPN in all patients diagnosed with ON and to distinguish the 2 by clinical course, radiologic appearance and treatment response.[67]

Inflammation of the optic nerve (ON) and its sheath (OPN) can have similar initial clinical presentations.[68] Both disorders present with symptoms of inflammatory optic neuropathies characterized by visual disturbances with signs of optic nerve dysfunction that include acute to subacute monocular vision loss (including color vision), pain with eye movement and a swollen or more often a normal-appearing optic disc.[67]

Regarding the demographics, OPN occurs in a broad age distribution with a majority of patients being over 50 years of age while ON tends to affect young adults with a female predominance.[67] Considering the tempo and pattern of vision loss, in OPN, the vision loss is usually peripheral or arcuate and progresses for several weeks. In ON, vision loss is usually central and/or altitudinal, occurs over several days, and is often self-limiting. For the associated symptoms, in OPN, there may be IOID-associated orbital

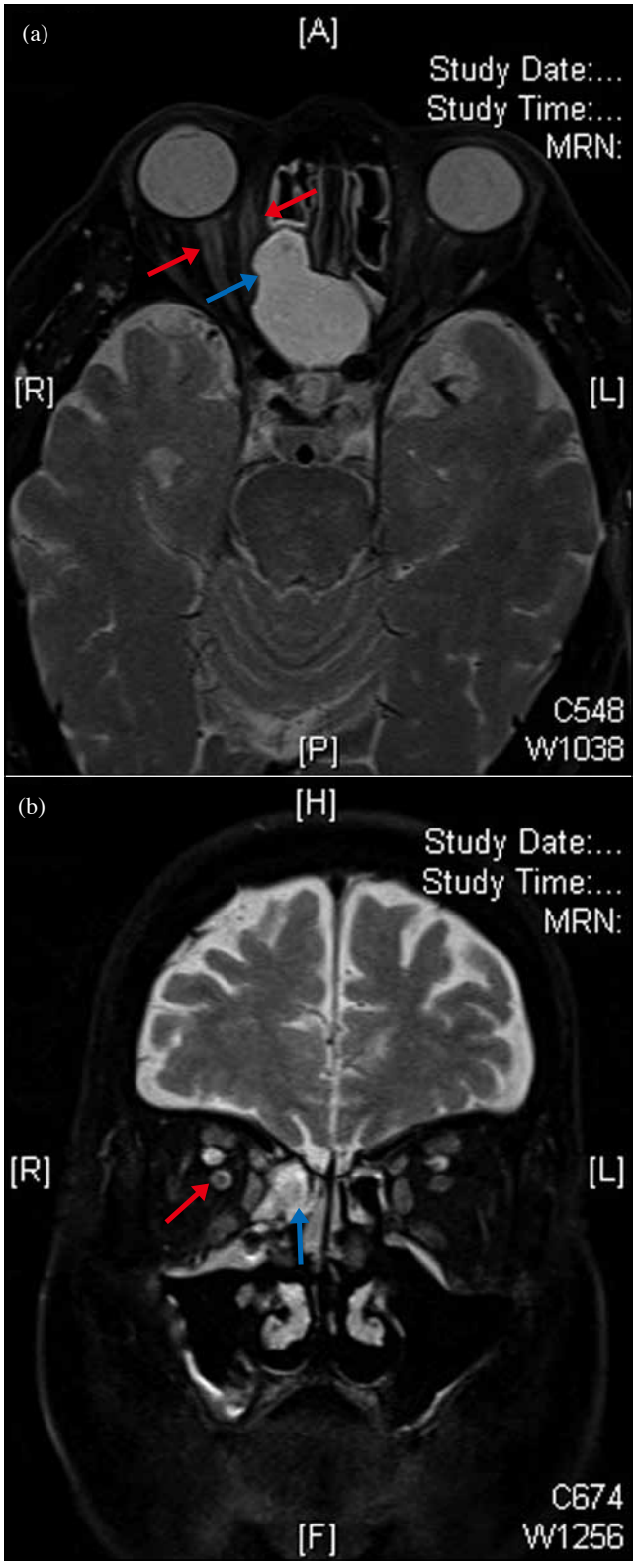

Figure 3. An 80-year-old male having right optic perineuritis after an episode of upper respiratory tract infection, with visual acuity down to light perception: T2 magnetic resonance imaging of the optic nerve demonstrates the (a) tram track sign (red arrows) and (b) donut sign (red arrow). There is a coincidental finding of mucocoele in the ethmoid sinus (blue arrows).

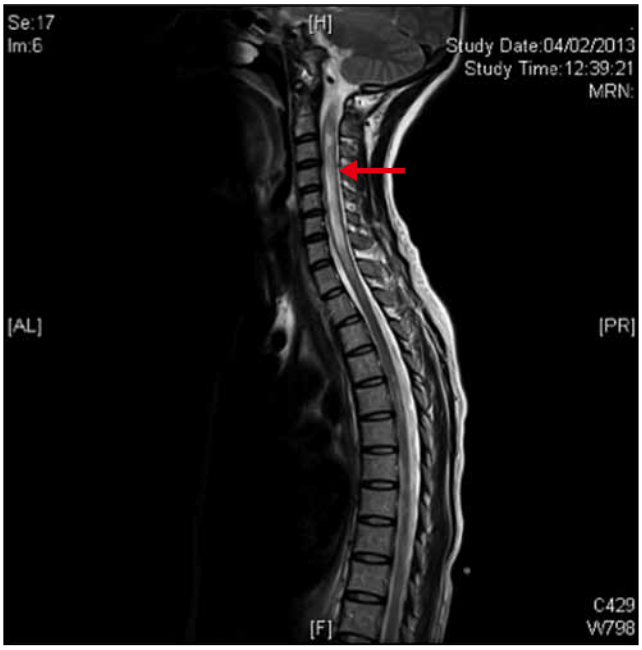

Figure 4. A 36-year-old female had recurrent episodes of optic neuritis and transverse myelitis, with positive aquaporin-4 antibody testing. She was wheelchair bound having visual acuity of hand movement in both eyes. The magnetic resonance imaging of her spine shows longitudinally extensive transverse myelitis (arrow). There is central gray matter involvement in the majority of the cervical spinal cord, and to a lesser extent in the thoracic spinal cord.

signs[69] in addition to the optic neuropathy, for example, mild motility disturbance secondary to extraocular muscle inflammation. These are not typical features of ON unless there is associated brainstem involvement due to multifocal demyelinating disease.[68] In ON, there may be other neurologic symptoms such as progressive limb weakness or ataxia that may indicate a more generalized pathology like MS.

Along with the clinical picture, a contrast MRI brain and orbit[68] should be performed as it can facilitate the differentiation of OPN from ON and help detect subtle orbital features and MS-related brain changes.[69] This is particularly important in patients with features such as those older than 45 years, sparing of central vision, vision loss that progresses for longer than 2 weeks, recurrence of pain and vision loss after discontinuation of corticosteroid therapy, pain out of proportion to vision loss, persistence of disc edema and evidence of orbital involvement (diplopia, subtle ptosis and chemosis).[68] It is worth noting that there should generally be a low threshold for neuro-imaging in Chinese patients to exclude OPN that is relatively more common.[69]

MRI findings can be grouped anatomically into perineural, intraneural and orbital. There is a characteristic pattern of enhancement around the optic nerve (i.e. in the optic nerve

Table 4. Comparison of MS-ON, NMO-ON and OPN.

	MS-ON	NMO-ON	OPN
Etiology	T-cell linkage problem causing demyelination	B-cell linkage problem, autoantibody-mediated inflammatory disorder	Idiopathic inflammation of dural sheath of the optic nerve
Demographics	(a) More common in Caucasians (b) Female predominance (3 times than male) (c) Association with higher latitudes	(a) More common in Chinese population (b) Female predominance	(a) More common in Chinese population (b) No sexual predominance
Median age (years) of presentation	30	40	Older (35% >50 years)
Clinical features	(a) Self-limiting mild vision loss with prominent dyschromatopsia and phosphenes over days, affecting central field (b) Periocular and retrobulbar pain on movement (c) Swollen optic disc (papillitis) in 1/3	(a) Profound and persistent vision loss (b) Isolated ON, with 20% having bilateral involvement (c) Painful tonic spasm—specific for NMO-ON (d) Altitudinal field deficits—specific for NMO-ON (e) Optic disc usually normal	(a) Progressive vision loss over weeks, affecting paracentral or arcuate field (b) IOID-associated orbital sign—diplopia, subtle ptosis and chemosis
Investigations	Contrast MRI brain and orbit (a) optic nerve—short-length contrast-enhancing lesion (b) brain—ovoid enhancing lesion and Dawson finger perpendicular to ventricles, with possible cortical and perivenous involvement (c) spinal cord—peripheral posterior involvement, T1 hypo-intensity is rare (d) OCT (RNFL)—atrophy especially in temporal quadrant (e) LP—raised CSF oligoclonal bands and mild CSF pleocytosis (lymphocytes)	Contrast MRI brain and orbit (a) optic nerve—long-length/posterior-chiasma contrast-enhancing lesions (b) brain—cloud-like enhancing lesion in periependymal area, with possible hemispheric and corticospinal tracts involvement (c) spinal cord—LETM ≥3 contiguous segment, with central/gray matter involvement, T1 hypo-intense acute lesion (**Figure 4**) (d) OCT (RNFL) (e) more marked loss than in MS-ON (>15 μm) (f) widespread RNFL atrophy in superior and inferior quadrants (g) LP—more prominent pleocytosis (neutrophils and eosinophils) (h) Serology—anti-AQP4-IgG sensitive and highly specific	Contrast MRI / CT brain and orbit (a) Perineural—'donut' and 'tram tack' sign (b) Intraneural—inflammation of intra-neural pial septa (c) Orbital—streaky enhancement of extraocular muscles and/or orbital fat
Treatment	Expectant or corticosteroid +/- immunomodulatory agents	Early high-dose (1 g/day) intravenous methylprednisolone +/- immunomodulatory agents for 3-5 years	Early prolonged high-dose oral corticosteroid, slow taper
Prognosis	Variable response to steroid; overall good prognosis and relapse uncommon	Delayed treatment associated with poor outcome; worse prognosis and recurrence common	Excellent response and visual outcome upon early withdrawal of corticosteroid; relapse common upon brief treatment

Abbreviations: AQP4 = aquaporin-4; CSF = cerebrospinal fluid; CT = computed tomography; IgG = immunoglobulin G; IOID = idiopathic orbital inflammatory disease; LETM = longitudinally extensive transverse myelitis; LP = lumbar puncture; MRI = magnetic resonance imaging; MS-ON = multiple sclerosis–associated optic neuritis; NMO-ON = neuromyelitis optica–associated optic neuritis; OCT = optical coherence tomography; ON = optic neuritis; OPN = optic perineuritis; RNFL = retinal nerve fiber layer.

sheath)—'tram track sign' and 'donut sign' on axial and coronal cuts (**Figure 3**); along with streaky enhancement of the extraocular muscles, sclera or orbital fat. In occasional cases there is intraneural enhancement due to inflammation of pial septa.[68,70] In contrast, ON tends to show enhancement of the optic nerve itself along with other features of demyelinating disease such as spinal lesions (in MS and NMO), and white matter changes in the brain (as in MS).[68]

Alternatively, contrast computed tomographic orbit may also give a hint to the diagnosis of OPN, by showing prominence and enhancement of the affected optic nerve and/or perineural tissues and streaky enhancement of the surrounding orbital fat.[69]

Distinguishing OPN from ON has important management and prognostic implications. Intravenous methylprednisolone (1 g/day) can be considered an initial treatment to cover both ON and OPN, especially if neuro-imaging is not readily available.[69] The speed of response to steroids can help distinguish the 2 conditions and hence guide future management. Early initiation of high-dose oral prednisone (e.g. 80 mg/day) and prolonged steroid treatment for OPN are essential to prevent irreversible vision loss and recurrent attacks.[68] Delay in initiating therapy with oral corticosteroids can result in vision loss, while a dramatic response upon

steroid initiation and a recurrence of pain and/or vision loss upon steroid tapering suggest a diagnosis of OPN. The prognosis for vision outcome in these patients is generally excellent if prompt diagnosis and treatment are given.

Regarding secondary causes, specific inflammatory and neoplastic entities such as sarcoidosis, lymphoma, leptomeningeal carcinomatosis and fungal infiltrations, may demonstrate a similar response to treatment. These disorders, however, soon declare themselves by demonstrating recurrence and progression without managing the underlying cause.[68]

Conclusion

MS-ON, NMO-ON and OPN have disparate pathogeneses and treatment responses. An accurate diagnosis is vital as misdiagnosis and maltreatment may result in poor ophthalmological and neurological outcome. Discriminators, in terms of demographics, clinical features, laboratory and imaging findings, are summarized in **Table 4**.

Declaration

All authors have disclosed no conflicts of interest.

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POSITION PAPER

Optimizing management of diabetic macular edema in Hong Kong: a collaborative position paper

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Abstract

Focal/grid laser photocoagulation therapy has been the mainstay of treatment for diabetic macular edema at least since the 1980s, but the standard of care has changed with the advent of agents that target vascular endothelial growth factor. It is widely agreed that anti–vascular endothelial growth factor agents are the preferred first-line option for patients with fovea-involving diabetic macular edema who are able to access anti–vascular endothelial growth factor therapy. However, dosing protocols for anti–vascular endothelial growth factor agents vary and may not be well understood, including when to consider adding or switching to alternative therapies, such as photocoagulation or corticosteroid treatment. In light of such recently changing treatment approaches, a panel of local retinal specialists and an international expert convened to evaluate the roles of anti–vascular endothelial growth factor agents, corticosteroids and laser therapy in the treatment of diabetic macular edema and to formulate a set of recommendations that aim to optimize diabetic macular edema management in Hong Kong. This document summarizes the panel's recommendations. The key recommendation for the treatment of diabetic macular edema that involves the fovea is that physicians consider adopting an early intensive anti–vascular endothelial growth factor dosing schedule followed by a deferred injection strategy for stability (either resolution of diabetic macular edema or stable diabetic macular edema no longer improving or worsening) after the first 6 months. This protocol has been shown to reduce long-term treatment burden in terms of the number of injections and clinical visits required, while maintaining, on average, excellent outcomes. However, the panel acknowledges that physicians need to consider cost and accessibility restrictions applicable to each patient and to adjust their treatment strategy accordingly.

Key words: Aflibercept; Diabetic retinopathy; Macular edema; Ranibizumab; Receptors, vascular endothelial growth factor

Introduction

Diabetic macular edema (DME) is a leading cause of vision loss, particularly among the working-age population.[1-3] DME arises from glucose-related damage to retinal capillaries.[2] The retinal tissue becomes hypoxic, increasing its expression of vascular endothelial growth factor (VEGF) that induces vascular leakage and neovascularization.[2,3] These leaking capillaries cause the macula to become swollen and thickened, thereby causing blurring of vision or metamorphopsia.[2]

An estimated 11% of patients with diabetes mellitus develop DME. While the overall prevalence of DME among patients with diabetes aged 20 to 79 years is approximately 7.5%, the risk increases over time.[4,5] Given the global diabetes epidemic, it is expected that the number of DME cases in Hong Kong will increase.[2] At present, approximately 10% of the population in Hong Kong aged 20 to 79 years, and 20% of those aged ≥65 years, have diabetes.[6,7] Moreover, a recent study of 174,532 patients with diabetes in Hong Kong revealed a prevalence of diabetic retinopathy of 39%; 9.8% of these patients had sight-threatening diabetic retinopathy, including DME.[8]

Controlling blood glucose levels, as well as comorbidities such as hypertension, are key components of diabetes management, including managing DME, but therapeutic interventions, including focal/grid laser photocoagulation therapy and anti-VEGF therapies also play important roles.[9] Corticosteroids, such as intravitreal triamcinolone acetonide and dexamethasone implants, may also be useful, particularly in pseudophakic eyes, but are not superior to anti-VEGF therapy.[9] Laser therapy reduces the risk of vision loss in DME and has been the mainstay of treatment for DME over the last few decades.[10] However, in recent years a number of clinical trials have clearly shown that vision can be stabilized in most patients, and even improved by 2 or more lines, in approximately half of those treated with anti-VEGF therapy, which has been shown to be superior, on average, to both laser and corticosteroid therapy.[2,11] Accordingly, anti-VEGF therapy is recommended as a first-line treatment option for fovea-involving DME in a number of international guidelines.[9,12,13] At present, there is no consensus regarding the optimal anti-VEGF dosing regimen; some dosing protocols suggest 5 loading doses administered monthly followed by a fixed 8-week dosing schedule; others suggest 3 loading doses administered monthly followed by top-up injections administered on a pro re nata (PRN) basis.[14,15] The Diabetic Retinopathy Clinical Research Network (DRCR.net) has advocated yet a different regimen.[11,16]

Given the wide variety of treatment options and dosing regimens available, physicians may require some guidance to determine the optimal management approach for their patients.

Methods

The decision to develop this position paper was made by a panel of local retinal specialists and an international expert on retinal and macular disorders. A meeting was convened on 21 March 2016 to formulate a set of recommendations to optimize DME management in Hong Kong. The recommendations were developed following a series of presentations and round-table discussions on the current status of DME therapy, and based on data from key clinical trials and evidence-based best practice approaches. This position paper and the recommendations contained within were reviewed and approved by all participants in May 2017.

Practice in Hong Kong in 2016

Before discussing recommendations from the panel, a summary was developed to describe ophthalmologists' current use of laser therapy and anti-VEGF therapies in Hong Kong. All participants agreed these were first-line treatments for most patients with DME. Corticosteroids were regarded as a suitable second-line therapy.

Discussion among the panelists indicated that physicians practicing in Hong Kong were administering anti-VEGF therapy according to a schedule of monthly intravitreal injections for 3 months among patients able to access such treatment. Further injections were administered PRN in response to further deterioration without specifically defining 'deterioration'. Laser photocoagulation was usually reserved for special cases where there was clear evidence of leakage from a microaneurysm surrounded by a circinate ring of lipid exudate, or if patients did not respond to, or could not afford, anti-VEGF therapy. Intravitreal corticosteroids were recommended for patients who had fovea-involving DME in eyes with no history of glaucoma or ocular infection that were pseudophakic, or with significant cataracts (for concurrent cataract extraction and intravitreal corticosteroid injection).

Treatment selection in Hong Kong was also influenced by waiting times for consultations, potential delays in receiving treatment and the lack of reimbursement for anti-VEGF therapy. Patients who cannot access anti-VEGF therapy often continue receiving laser therapy.

The evidence supporting the use of currently available pharmacologic treatment options and their use in Hong Kong is reviewed below.

Anti–vascular endothelial growth factor therapy

Ranibizumab

The safety and efficacy of anti-VEGF therapy in DME was first established based on studies that compared ranibizumab with sham/laser photocoagulation. Data from the RISE and RIDE studies indicate that vision loss associated with DME may be reversed and clinically significant improvement

in visual acuity is achieved with monthly anti-VEGF therapy over several years.[17] A significantly greater proportion of patients treated with monthly injections of intravitreal ranibizumab 0.3 mg or 0.5 mg achieved a ≥15 Early Treatment Diabetic Retinopathy Study letter gain at 24 months than patients administered sham injections in both trials. These improvements were also associated with reductions in central subfield thickness (CST) on optical coherence tomography (OCT).[17]

Ranibizumab as monotherapy, or in combination with laser therapy, was also superior to laser monotherapy in improving the mean change in best-corrected visual acuity (BCVA) letter score from baseline through 12 months in the RESTORE study.[18] The changes in BCVA from baseline were accompanied by an improvement in OCT CST from baseline.[18] There were no definitive efficacy differences detected between the ranibizumab and combination arms with respect to improvement in BCVA or the number of injections required.[18] The functional and anatomic improvements with ranibizumab were maintained for at least 3 years with patients requiring fewer injections each year.[19]

The DRCR.net Protocol I study provided further long-term data over 5 years that ranibizumab combined with prompt or deferred (≥24 weeks) focal/grid laser could improve visual acuity compared with the standard treatment for DME of laser alone.[11] Nonetheless, these outcomes only required monthly treatment for the first 6 months with one exception, if the OCT CST was not thickened abnormally or the visual acuity was 20/20 or better at 2 consecutive injections following at least 4 injections. This latter circumstance was the exception rather than the rule, so essentially, most eyes received 6 initial monthly injections. After 6 months, ranibizumab was continued only if there was improvement of OCT CST of at least 10%, or of visual acuity of at least 5 letters, compared with the last 2 consecutive injections. Otherwise, injections were withheld, even if there was persistent but stable DME. Once injections were withheld, if DME CST or visual acuity worsened, injections were resumed. Focal/grid laser was added in persistent but stable DME after 6 monthly injections if there were treatable lesions and at least 4 months had passed since any prior laser treatment. If the condition is stable without injections after 1 year, follow-up could be extended to at least every 2 months and if remaining stable, extended to every 4 months. This approach resulted in sustained visual acuity gains through 5 years with only about 40% requiring any focal/grid laser, usually only once or twice, and with a decreasing number of injections and visits in years 2, 3, 4 and 5.[20]

Aflibercept

Intravitreal aflibercept 2 mg significantly improved vision outcomes and reduced rates of severe vision loss compared with laser monotherapy in the VIVID and VISTA studies.[21] Patients were randomized to monthly intravitreal injections of aflibercept 2 mg for 5 months plus further injections administered on a monthly or bimonthly basis or laser photocoagulation.[21] Both studies also showed that aflibercept achieved superior functional and anatomic outcomes to laser therapy.[21]

The DRCR.net Protocol T study showed that aflibercept 2 mg, bevacizumab 1.25 mg and ranibizumab 0.3 mg generally have comparable efficacy, on average, in patients with mild vision loss (20/32 to 20/40) related to DME. Aflibercept, however, was more effective in improving vision in patients with lower baseline levels of visual acuity at 1 year (baseline letter score <69, equivalent to 20/50 or worse), and compared with bevacizumab at 2 years, following the same regimen as described for Protocol I, at 1 year, with 2 exceptions. First, injections within the first 6 months could be withheld only if both the OCT CST were not thickened and the visual acuity was 20/20 or better; this occurred typically in <5% of the participants in any treatment group. Second, if the OCT CST thickened, or visual acuity worsened, after withholding injections after 6 months, resumption of injections was required rather than recommended.[16] The superiority of aflibercept observed after 1 year contributed to the superiority of aflibercept over bevacizumab or ranibizumab when assessed over 2 years using a post-hoc analysis of the area under the curve for a mean change in visual acuity from baseline.[22,23] At the 2-year time-point itself, aflibercept was superior to bevacizumab, but not ranibizumab across clinically relevant secondary outcomes, including improvement of at least 15 letters from baseline.[22]

Intravitreal steroids

Dexamethasone implant

Intravitreal steroid therapy may have both anti-angiogenic and anti-inflammatory activity. The efficacy and safety of steroid therapy for DME was confirmed in the MEAD study in which significantly more dexamethasone-treated patients (0.70 mg intravitreal implant or 0.35 mg intravitreal implant) achieved a BCVA of ≥15 letters at 3 years compared with those who received the sham implant.[24] Moreover, fewer patients who received dexamethasone 0.70 mg experienced a ≥15 letter loss in BCVA compared with patients receiving a sham implant.[24] There was substantial loss to follow-up, however, and it is unknown how these outcomes would compare with focal/grid laser instead of no (sham) treatment in an intent-to-treat analysis over 3 years.[24] During the second year of treatment, dexamethasone was also associated with an increased risk of cataracts. This may have correlated with reduced treatment efficacy, even after the cataracts were removed, if permanent visual acuity loss occurred in some eyes either from exacerbation of DME or post-surgical cystoid macular edema, or both, following cataract surgery in the setting of DME.[24,25]

Furthermore, a comparable proportion of patients with DME achieved a BCVA improvement of ≥10 letters in a head-to-head comparison of a dexamethasone implant (0.7 mg PRN; maximum of once every 16 weeks) with anti-VEGF therapy

(bevacizumab 1.25 mg PRN; maximum of once every 4 weeks) in the BEVORDEX study, although vision loss of ≥10 letters was more common among the dexamethasone-treated eyes, mainly because of cataracts.[26] Despite this, dexamethasone implants might be considered a first-line therapy in vitrectomized DME eyes that frequently fail to respond to anti-VEGF therapy.[27,28]

Intravitreal triamcinolone acetonide

Intravitreal triamcinolone acetonide combined with prompt laser therapy was superior to laser therapy alone in a subgroup of patients with pseudophakic eyes. The response was comparable with ranibizumab in these patients through the 2-year follow-up visit,[11] but not at 5 years.[29] Also, 45% of eyes in the corticosteroid group had adverse events related to intraocular pressure compared with approximately 10% in the focal/grid laser group or anti-VEGF groups.[30]

Optimizing management of diabetic macular edema: latest evidence from DRCR.net studies

The most recent data from studies conducted by the DRCR.net, a collaborative multicenter network involving more than 400 physicians throughout the United States, indicate that initiating treatment with monthly injections of anti-VEGF therapy over the first 6 months (with one exception as described above that occurred in fewer than 5% of patients) with a median of 3 additional treatments administered during the following 6 months, and a median of 5 treatments in the second year, accompanied by subsequent laser therapy for any persistent DME with treatable lesions, maximizes clinical outcomes for patients with DME.[16]

Treating patients with persistent macular thickening

The DRCR.net Protocol I study showed that approximately 40% of patients with DME display persistent macular thickening after 6 months of anti-VEGF therapy.[31] For patients with persistent DME, a treatment protocol of as-needed anti-VEGF injections from month 6 to month 12 with deferred laser and monthly follow-up, and as-needed anti-VEGF injections after 12 months with follow-up extended to every 2 to 4 months, based on CST or visual acuity, may be adopted as a standard treatment.[31]

Data collected after 3 years of follow-up of patients being administered this protocol indicated that abnormal thickening had resolved in 60% of patients, and vision improved (>10 letters gain) in 43%, after a similar number of injections in patients without persistent macular thickening.[31] Moreover substantial (≥2 line) vision loss was uncommon despite chronic persistent DME after initiating anti-VEGF treatment.[31] While it remains unknown how these eyes would have fared with other regimens, including anti-VEGF injections every month or every 2 months, or switching between anti-VEGF agents or to other regimens such as corticosteroids, the results with the DRCR.net regimen and no switching suggest a high likelihood of successful outcomes and represent a high bar for any alternative regimen to achieve.

Long-term management of diabetic macular edema with anti–vascular endothelial growth factor and laser therapy

In the DRCR.net Protocol I study, patients received anti-VEGF therapy every 4 weeks until no further improvement were observed (with resumption, if worsening) and either prompt or deferred (≥24 weeks) focal/grid laser treatments.[11,20] After the first year of the study, there was a substantial decrease in the frequency of injections in all patients.[20] In year 4, only half of the study population treated required at least one injection and by year 5, more than half of the patient population did not require any injections.[20] Vision improvements achieved with anti-VEGF and laser therapy in the first year were maintained through year 5, despite the reduced need for subsequent intravitreal anti-VEGF injection.[20,32] Visual acuity among patients who received prompt laser therapy was no better (and in some cases, even worse) than that among patients who received deferred therapy.[20,32]

Analyses performed after 2 years of follow-up in the DRCR.net Protocol T study revealed that visual acuity improvements were maintained with all 3 anti-VEGF agents (aflibercept, ranibizumab and bevacizumab), but greater improvements were observed in those whose vision was worse at baseline.[22] In particular, over 2 years of treatment, aflibercept appeared to offer a greater benefit (area under the curve) than the other anti-VEGF therapies in patients with a baseline visual acuity of 20/50 or worse.[23] Similar to the DRCR.net Protocol I study, patients only received frequent anti-VEGF injections in the first year with a median of 9 to 10 injections; this was reduced by around half to a median of 5 to 6 injections during year 2 with the DRCR.net treatment regimen for DME.[22]

Position statements and recommendations from the collaborative expert panel

- An optimal DME management regimen should be initiated using monthly anti-VEGF injections for the first 6 months to achieve maximum visual acuity improvement. One exception might be if the case was 'perfect' after 2 consecutive injections, including both visual acuity of 20/20 or better and an OCT CST that appeared normal, recognizing that such exceptions might occur in approximately 5% of patients being treated.
- Patients should be monitored on a monthly basis after the first 6 months of treatment through 1 year as worsening of visual acuity from DME, or worsening of DME CST, often occurs; then incremental increases in treatment intervals can be employed starting at 1 year, first to every 2 months, then every 4 months, unless worsening warrants resumption of anti-VEGF injections with monthly follow-up until stable again. This strategy aims to identify the longest possible treatment-free

interval for each patient, potentially extending the interval between anti-VEGF treatments and improving patient compliance.

- Addition of focal/grid laser photocoagulation may be considered in patients who have persistent, stable edema despite anti-VEGF injections after 6 months, provided there are lesions to treat and treatment is no more than every 4 months.
- Switching to other agents may be considered in patients with persistent macular thickening and deteriorating vision after initiating anti-VEGF therapy for 12 months and after using laser therapy after 6 months for persistent DME, recognizing that without switching, excellent results, per the DRCR.net outcomes, may still be achieved. It is unknown if such switching results in as good or better outcomes than not switching.
- A defer-and-extend approach (e.g. treatment regimens used in DRCR.net Protocols I and T) may be considered after 12 months to maintain vision and reduce subsequent injection burden, although evidence to support this approach is currently lacking.
- DME and choroidal neovascular ('wet') age-related macular degeneration should be considered differently; regimens proven beneficial for DME may not apply to choroidal neovascular age-related macular degeneration.

The treatment algorithm suggested by the collaborative expert panel is shown in the **Figure**.

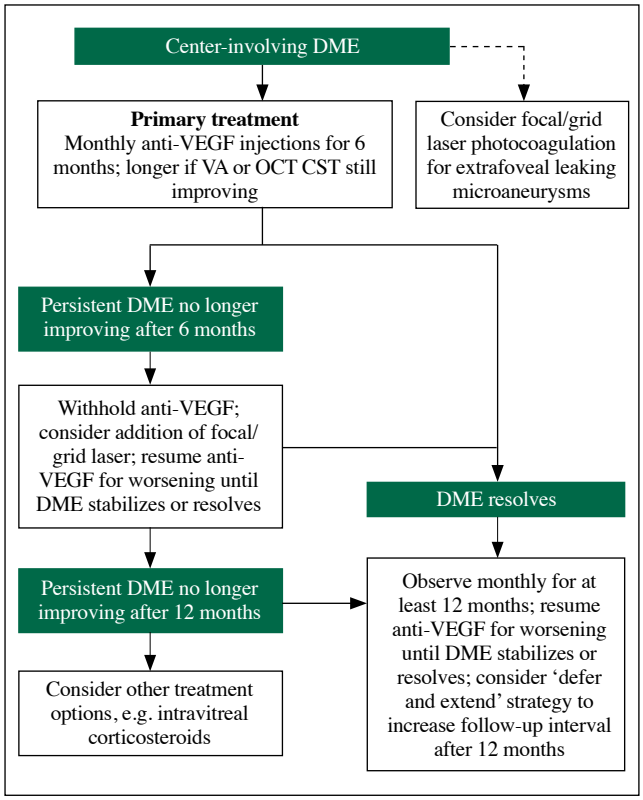

Figure. Suggested treatment algorithm for center-involving DME.*

Abbreviations: DME = diabetic macular edema; OCT CST = central subfield thickness on optical coherence tomography; VA = visual acuity; VEGF = vascular endothelial growth factor.

** Presumes no limitations on treatment resources.*

Conclusion

Anti-VEGF therapy has led to a paradigm shift in the treatment of DME and offers a superior first-line therapy to laser photocoagulation. Recent data suggest that current practice in Hong Kong, as performed in 2016, may not be optimal because the majority of patients with DME who are treated with anti-VEGF therapies receive suboptimal loading-dose injections. The panel recommends that patients who have access to anti-VEGF treatment attempt to maximize their vision improvement through more intensive anti-VEGF loading-dose injections at treatment initiation, for example, starting with 6-monthly injections unless it becomes 'perfect' following 2 consecutive injections. While this may initially appear to increase the treatment cost, it may be the most cost-effective approach in the long term. Patients who receive this number of initial loading-dose injections generally require fewer subsequent injections due to improved long-term vision stability. A deferred injection approach, when indicated per the DRCR.net treatment regimen, can also be adopted after the first 6 months of anti-VEGF treatment, reducing the number of injections and clinic visits required in subsequent years. This strategy may be particularly useful for patients in Hong Kong given the long waiting times and high volume of patients who require treatment. However, regular visual acuity and OCT monitoring is still required. Ultimately, physicians need to consider each patient on an individual basis and adjust their approach based on the patient's visual acuity at baseline, possible co-existing medical conditions that affect their vision and their ability to access treatment.

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Declaration

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CASE REPORT

Orbital exenteration: surgery, treatment outcome and rehabilitation

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Abstract

We report on three patients who underwent orbital exenteration from June 2011 to June 2016 at United Christian Hospital, Hong Kong. We aimed to illustrate the surgical techniques of orbital exenteration, the treatment and the rehabilitation. Healing by primary granulation and epithelialization has the advantage of avoiding tumor or disease recurrence being masked. Ocular prosthesis was provided to achieve good cosmetic outcome. In conclusion, orbital exenteration is a major surgery indicated in non-salvagable ocular disease. In good hands, surgery can provide good anatomic and cosmetic outcome.

Key words: Orbit evisceration; Reconstructive surgical procedures; Treatment outcome; Wound healing/physiology

Introduction

Orbital exenteration, first described by George Bartisch in 1583,[1] is defined as surgical removal of the globe and the affected orbital contents, including orbital fat, conjunctival sac, with or without the eyelids.[2] It is the most radical type of eye amputation, reserved as a curative treatment for potentially life-threatening locally invasive malignancies, or to aid in palliation of blind painful eye or severe deformity, or less often as a treatment for non-malignant disease.[3] We present a case series of 3 patients who underwent orbital exenteration at United Christian Hospital, Hong Kong from June 2011 to June 2016. Surgical techniques, the treatment outcome and the rehabilitation are illustrated.

Case reports

Case 1 (sebaceous cell carcinoma, illustrating surgical techniques)

An 84-year-old female with a history of severe tricuspid regurgitation and bilateral total knee replacement presented with recurrent left upper lid chalazion in April 2010 (**Figure 1a**). Multiple incision and curettage was performed but the lesion recurred. Excisional biopsy was performed in April 2013 and the pathologic diagnosis was poorly differentiated carcinoma. Computed tomography (CT) imaging of the orbit showed a contrast enhanced lesion at the left upper outer eyelid, compatible with the biopsy-proven carcinoma. The patient refused any further surgical intervention in view of her advanced age and comorbidities. Radiotherapy was therefore arranged in July and August 2013 but the lesion did not regress. Another excisional biopsy in December 2014 confirmed a pathologic diagnosis of sebaceous cell carcinoma. The patient was informed of the aggressive nature of the disease but still refused surgical treatment. She consented to undergo only left upper lid mass debulking and cryotherapy under local anesthesia that was performed in September 2015. After a long course of counseling and regular follow-up at the oculoplastic outpatient clinic, she finally agreed to undergo orbital exenteration. Contrast CT of the brain, orbit, thorax, abdomen and pelvis confirmed no distant metastasis. Orbital exenteration was performed in June 2016 (**Figure 1b**).

Surgery was performed under general anesthesia and the surgical steps of exenteration are detailed in **Figure 2**.

Case 2 (apocrine carcinoma, illustrating healing process by granulation)

A 67-year-old man with a history of hypertension presented in August 2012 with right lower lid induration for 1 year

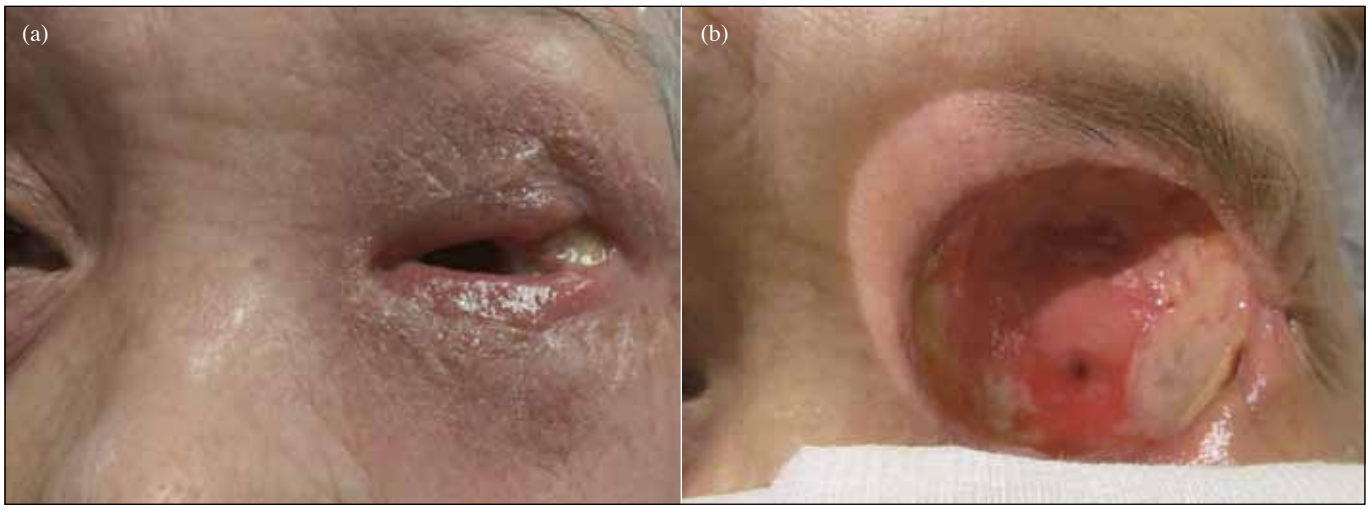

Figure 1. Case 1: (a) left upper eyelid cancer with invasion into surrounding periocular tissue; and (b) an orbital socket with granulation 2 months after the operation.

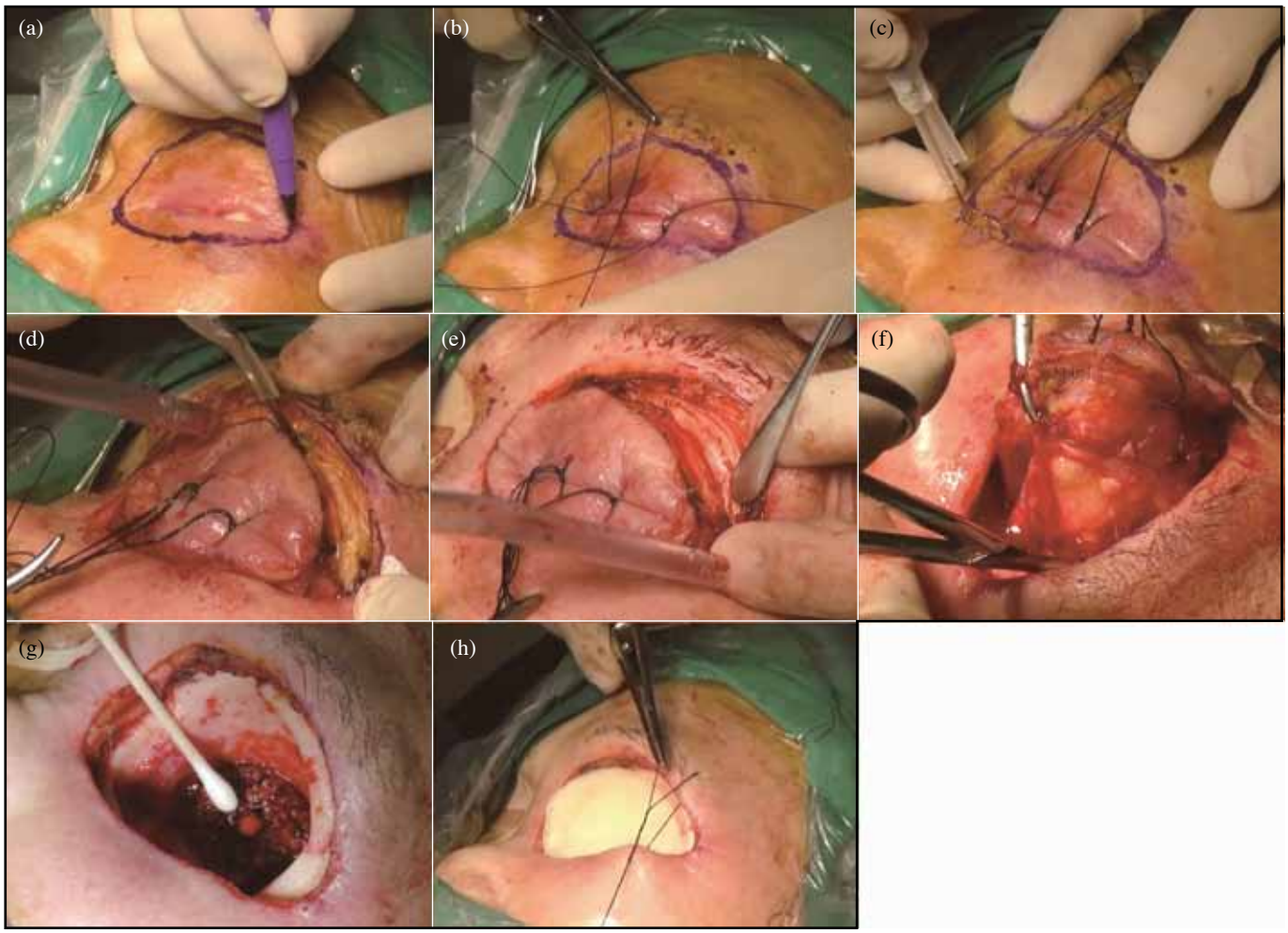

Figure 2. Case 1: the surgical steps of exenteration. (a) The orbital rim is marked by skin marker. (b) Eyelids are closed with traction sutures inserted. (c) Skin incision is made along the marked area using cutting diathermy. (d) Dissection is made through the periorbital to expose the orbital rim. (e) The periosteum is incised for 360 degrees and the reflected periosterum is elevated from orbital wall. (f) Orbital tissues are divided at the apex. (g) Completion of exenteration with hemostasis achieved. (h) The socket is dressed with paraffin gauze and skin aperture closed with suture.

(**Figure 3a**). CT revealed a lobulated mass at the medial and inferior parts of the right orbit, abutting on the globe and infiltrating the right lower lid and lacrimal sac. Incisional biopsy of the mass in October 2012 yielded a pathologic diagnosis of adenocarcinoma with lymphatic permeation. Positron emission tomography confirmed no distant metastasis. Right orbital exenteration was performed in December 2012. The exenterated tissue was sent for histologic analysis and confirmed the diagnosis of apocrine carcinoma. Adjuvant radiotherapy was completed in March 2013. In April 2014, upon routine regular monitoring, a submandibular lymph node was noted. Ultrasound-guided fine-needle aspiration confirmed metastatic adenocarcinoma. Right modified radical neck dissection with superficial parotidectomy was performed in May 2014 and adjuvant radiotherapy was completed in September 2014.

A series of clinical pictures after orbital exenteration is shown (**Figures 3b** to **3f**). The granulation process required approximately 4 months to complete and is compatible with data from the literature.[3]

Case 3 (nasopharyngeal carcinoma, illustrating rehabilitation possibilities)

A 49-year-old man with a history of endoscopic dacryocystorhinostomy (EDCR) performed for nasolacrimal duct obstruction in 2005, presented with vertical diplopia in 2010. He was found to have right hypertropia on examination, initially suspicious of right fourth cranial nerve palsy. CT orbit found a right inner canthus mass with bone erosion. The nasal mucosa and previous EDCR site was biopsied and pathology was undifferentiated carcinoma at nasolacrimal sac. Orbital exenteration with open

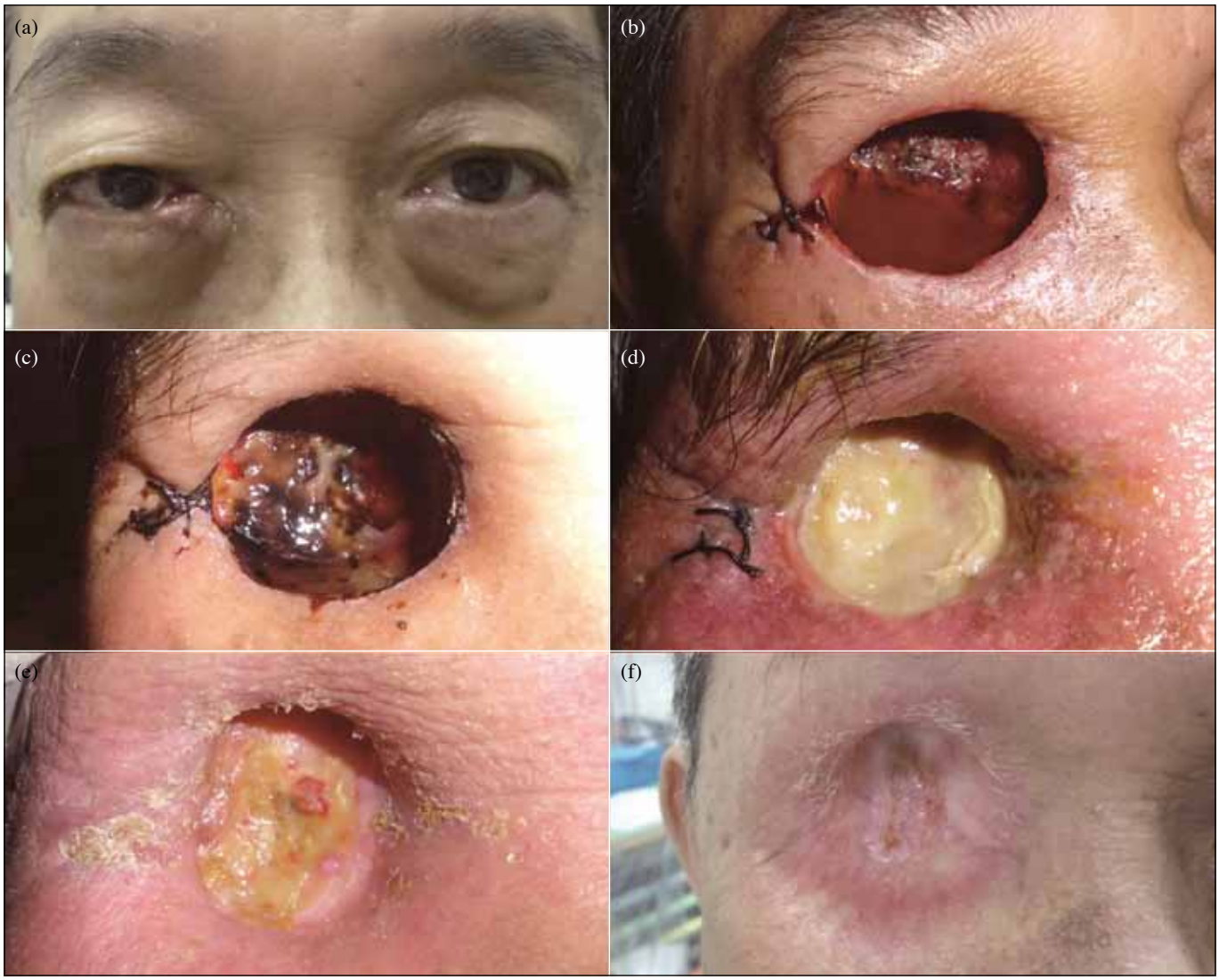

Figure 3. Case 2: (a) A right lower lid mass near the medial canthus before operation. Postoperative clinical photographs showing (b) mild oozing on day 3, (c) necrotic slough at the base of socket at 2 weeks, (d) thick yellowish slough at base of wound at 2.5 months, (e) dried slough with granulation tissue at the base of the wound at 4 months and (f) scarring and completion of the granulation process at 15 months.

maxillectomy was carried out in July 2011. The anterior and posterior margins were involved and adjuvant radiotherapy was completed in November 2011.

He was referred to a maxillofacial prosthodontist for rehabilitation with artificial prosthesis, and he started using the orbital prosthesis 1 year after exenteration. He was first given a silicone intrinsic pack, which is a type of adhesive retained prosthesis (**Figure 4a**). With time, wear and tear of the prosthesis caused frequent dislodgment. Hence the prosthodontist created a self-retaining implant based on the idea of osseointegrated implants. The external eye piece was secured onto the self-retaining device with magnets (**Figure 4b**).

Discussion

Exenteration can be classified as total, subtotal or extended; subtotal exenteration spares either or both the eyelids and the conjunctiva, and the extended type removes also the diseased bone or soft tissue. Although subtotal exenteration offers a better cosmetic outcome, faster healing and less chance of sino-orbital fistula formation, it should not be chosen at the expense of a complete surgical cure.

The most common indication for orbital exenteration is orbital invasion by periocular cutaneous malignant tumors, of which 90% are basal cell carcinoma.[4-9] Orbital invasion can present with mass effect such as globe displacement or ptosis, or signs of tissue infiltration including restricted ocular motility, immobile eyelids or fixation of the tumor to bone.[8] When these signs are present, orbital exenteration is deemed necessary, be it for curative or palliative intent. The surgical specimen should be sent for checking of margin involvement, although a clear margin does not necessarily indicate a complete cure.[10,11]

Reconstruction methods may be local, regional or locoregional. All our 3 cases healed by secondary intention, in other words spontaneous granulation. The advantage is that local recurrence of malignancy can be picked up early, and patients can commence radiotherapy. The disadvantages include frequent need for wound dressing and socket care, a longer course to complete healing and a potentially higher

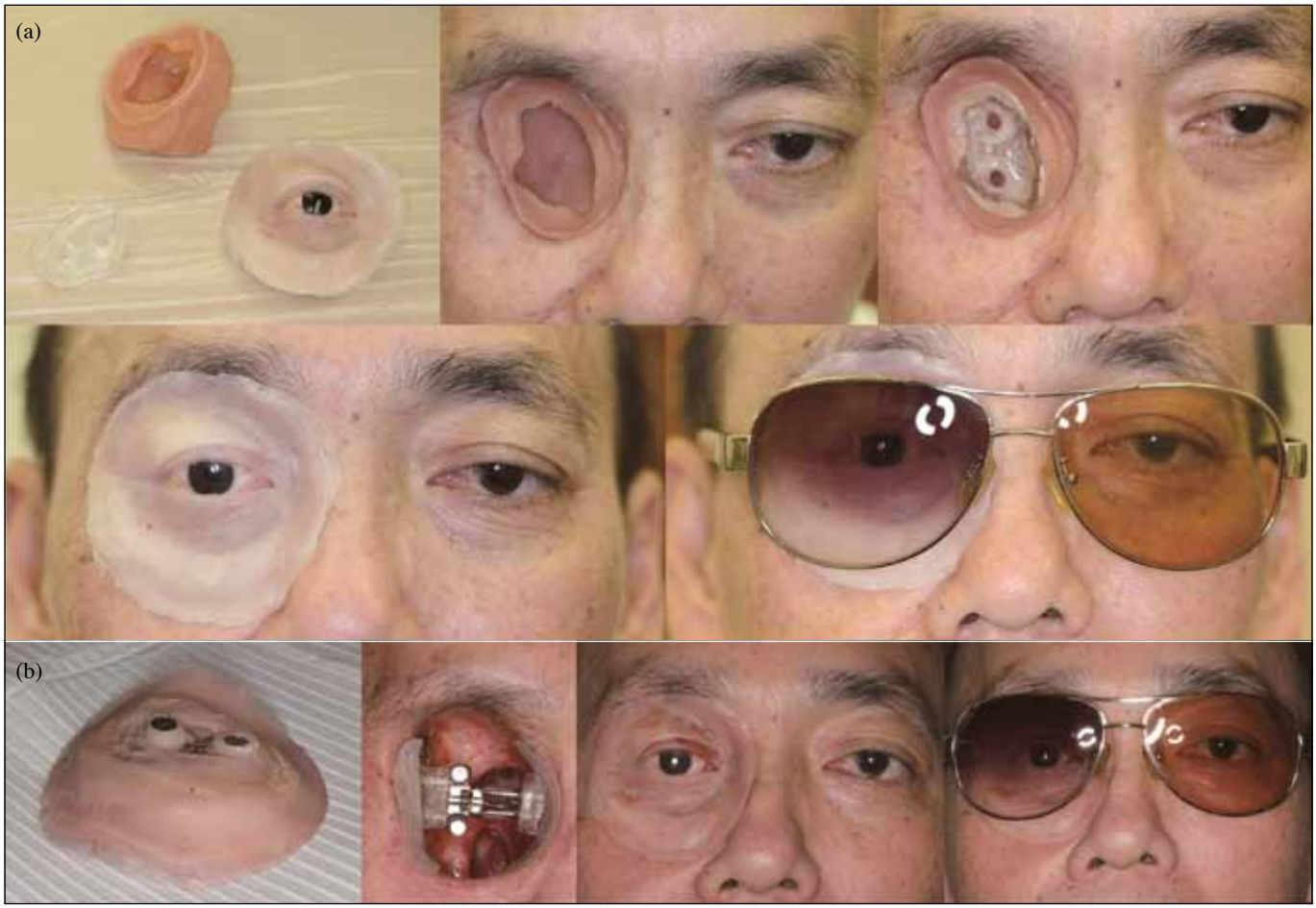

Figure 4. Case 3: Clinical photographs showing (a) the silicone intrinsic pack comprising 3 components: a silicone elastomer as the base, a connector and the external prosthesis. The 3 pieces merge to form the final silicone prosthesis after being inserted into the patient's socket in turn; and (b) the self-retaining device with a magnetic counterpart to secure the external eye piece.

Table. Summary of the 3 cases.

Case No.	Age (years) at operation	Gender	Presenting symptom	Histopathologic diagnosis	Hospital stay (days)	Time of disease till procedure (months)	Other treatment	No. of procedures related to current lesion
1	84	F	Recurrent LUL chalazion	Sebaceous cell carcinoma	17	39	Radiotherapy	7
2	67	M	RLL indurated mass for 1 year	Apocrine carcinoma	6	2	Radiotherapy	2
3	49	M	Vertical diplopia	Nasopharyngeal carcinoma	11	8	Radiotherapy	3

Abbreviations: LUL = left upper eyelid; RLL = right lower eyelid.

risk of developing sino-orbital fistulas.

Patients can choose between a spectacles-retained, adhesive-retained or implant-retained prosthesis. Spectacles-retained prosthesis, as its name suggests, is an oculofacial prosthesis that can be mounted on the spectacles frame. The advantages of using this type of prosthesis are that it is economical, user-friendly, and easily placed or removed by the patient.[12] The prosthesis, however, can be quite heavy and bulky, and patients need to wear glasses if they wish to use the prosthesis; in other words they cannot remove their spectacles in public.[3,12] Patients may then lose confidence with this type of prosthesis and may consider using an eye patch instead.[4]

An adhesive-retained prosthesis is attached to the patient's sockets by adhesives in the form of tapes, creams or sprays.[12] The advantage is that patients do not have to wear glasses while using the prosthesis, but it may not be appropriate for those who are allergic to the adhesives or who have sensitive skin. It is also not desirable for unhealed sockets or wounds that heal with exudates. Misalignment is also another drawback.[13,14] It may not be possible for patients who have bilateral exenteration, as it requires manual dexterity and vision for correct orientation of the prosthesis and daily application and removal of the prosthesis.[12]

An implant-retained prosthesis means the prosthesis is attached by magnets or clips to the titanium osseointegrated implant in the socket.[3] The advantages are that it is economical with a longer shelf life, less affected by sweat or UV light,[15,16] and does not require the use of spectacles or adhesives yet can still provide satisfactory retention.[12] The disadvantages include increased expense and the need for 2-stage surgery; it is also not appropriate for patients who have received postoperative radiotherapy. The risk of soft tissue infection is higher and brings a higher failure rate.[12,17] Patients also need to have a certain degree of manual dexterity to position the prosthesis correctly, although this can be learnt with time.[12] Another drawback is corrosion or loss of magnetism.[18]

Our patient in case 3 started using his implant-retained prosthesis 1 year after orbital exenteration and is enjoying a satisfactory cosmetic outcome.

Conclusion

Orbital exenteration was performed for malignancy in all our 3 cases with their summary shown in the **Table**. As it is both psychologically and anatomically disfiguring, it is considered the last resort when conservative excision is unlikely to achieve complete clearance.[3] Good surgical techniques as well as collaborative treatment with an oncologist are necessary to prevent metastasis. Rehabilitation with an orbital prosthesis provides a superior aesthetic effect.

Declaration

All authors have disclosed no conflicts of interest.

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