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[a]Values for ALTAIR represent 2-week dosing schedules at 52 and 96 weeks.
[b]Primary endpoint was mean change in BCVA (ETDRS letters) from baseline up to 52 weeks.
BCVA=best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study;
nAMD=neovascular age-related macular degeneration

References: 1. EYLEA® (aflibercept solution for injection) Full Prescribing Information. Hong Kong June 2019. **2.** Ohji M, Okada AA, Kobayashi M, et al. Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend Regimens in Exudative Age-Related Macular Degeneration: 52- and 96-Week Findings from ALTAIR: A Randomized Controlled Trial. *Adv Ther* 37, 1173–1187 (2020).

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- The *Hong Kong Journal of Ophthalmology* (HKJO) is the official publication of the College of Ophthalmologists of Hong Kong. The Journal aims to promote academic developments in ophthalmology, and to maintain continuing ophthalmological education of doctors of this specialty and other related disciplines. It is hoped that through achieving these aims, the quality of eyecare we offer to our patients can be lifted to new heights. The Journal will consider any submissions that fulfill these aims for publication.
- The Journal accepts high-quality submissions in the following categories: Original Article, Review, Perspective, Case Report, Photo Essay, Clinical Quiz, or Letter to the Editor. Editorials are by invitation only.
- The Journal is circulated to all members of the College of Ophthalmologists of Hong Kong and other professional societies and academic institutions in Hong Kong and internationally.

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香 港 眼 科 醫 學 院

THE HONG KONG JOURNAL OF OPHTHALMOLOGY
BEST ORIGINAL ARTICLE AWARD

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).

Awards and Prizes

Two awards will be given out every year. Each awardee will be given a $2000 cash prize (HK dollars), which is supported generously by the Timothy KC Liu Fund.

Eligibility

- One award is open to all fellows and members of the College; another one is limited to trainees only.
- 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 or 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).

Selection Panel

- Editor-in-Chief
- 1 representative from the University of Hong Kong
- 1 representative from the Chinese University of Hong Kong and
- President of the College

Selection Criteria

- Originality
- Scientific merit
- Methodology
- Presentation style

Award Presentation Ceremony

The awards will be given out at the following year's conferment ceremony.

Treatment of wet and dry types of age-related macular degeneration

Age-related macular degeneration (AMD) is a common cause of blindness in developed regions.[1] Late-stage AMD is categorized as the neovascular (wet) type and the atrophic (dry) type. Despite the availability of several potent drugs for the treatment of wet-type AMD, the problem of reducing treatment burden and enhancing treatment compliance remains a challenge. No proven treatments are available for dry-type AMD.

In this issue of the *Hong Kong Journal of Ophthalmology*, Kwok et al[2] report the 2020 updates on recommendations for the treat-and-extend regimen for wet-type AMD. The authors recommend maintenance of treatment if there is no loss of ≥5 ETDRS (Early Treatment Diabetic Retinopathy Study) letters, decreased intraretinal fluid, stable residual subretinal fluid ≤200 μm, no new macular hemorrhage, and no new neovascularization. The recommended criteria for extension or reduction of treatment can readily be derived from these maintenance criteria.

Also in this issue, Wong and Kwok[3] review emerging treatments for dry-type AMD with geographic atrophy (GA). Both a phase 2 trial of a C3 inhibitor (intravitreal pegcetacoplan) and a phase 3 trial of a C5 inhibitor (intravitreal avacincaptad pegol) show positive results. Furthermore, results of two phase 3 trials of the C3 inhibitor (pegcetacoplan) have recently been announced by the manufacturer and presented orally at the Annual Meeting of the American Academy of Ophthalmology.[4] The DERBY (621 patients enrolled) and OAKS (637 patients enrolled) trials are multicenter randomized double-masked sham-controlled studies of the efficacy and safety of intravitreal pegcetacoplan in patients with GA secondary to AMD. After 12 months of monthly or every-other-month treatment with pegcetacoplan, OAKS showed a reduction in GA lesion growth of 22% (p=0.0003) and 16% (p=0.0052), respectively, whereas DERBY showed a reduction of 12% (p=0.0528) and 11% (p=0.0750), respectively, but did not meet the primary endpoint of GA lesion growth. Nonetheless, in a prespecified analysis of the combined studies, pegcetacoplan was shown to decrease GA lesion growth in patients with extrafoveal lesions by 26% (p<0.0001) after monthly treatment and 23% (p=0.0002) after every-other-month treatment. We look forward to formal peer-reviewed publication of the results of these trials.

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ORIGINAL ARTICLE

Refixation of dislocated intraocular lens using the double needle flanged technique

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Abstract

Purpose: To review cases of refixation of the dislocated three-piece intraocular lens (IOL) using the Yamane flanged technique.
Methods: Medical charts of six patients who underwent refixation of subluxed or posteriorly dislocated three-piece IOLs using the Yamane flanged technique between January and December 2018 were retrospectively reviewed. The time from initial IOL implantation to IOL refixation, logMAR best-corrected visual acuity at baseline and months 1, 3, and 6, spherical equivalent at month 6, IOL horizontal and vertical tilt at month 6, and complications were documented.
Results: The mean time from IOL implantation to IOL refixation was 12.6±9.7 years. Of the six cases, four had successful refixation of IOL and two had unsuccessful refixation of IOL and necessitated removal of the IOL and implantation of a new one. The mean logMAR best-corrected visual acuity improved from 1.48 preoperatively to 0.680 at month 1, 0.400 at month 3, and 0.320 at month 6. The mean spherical equivalent at month 6 was -0.520. In the four cases with the original IOL, at month 6 the IOL horizontal tilt was 2.5°±4.5° and the vertical tilt was -4.00°±2.754°.
Conclusion: Using the Yamane flanged technique to refixate the dislocated IOL achieves good stability and spherical equivalent of the IOL. Intra-operative assessment of the IOL and correct angulation and manipulation of the haptics are crucial for the success of surgery.

Key words: Lens implantation, intraocular; Lens subluxation

Introduction

Intraocular lens (IOL) dislocation is a serious complication after cataract surgery, with an incidence ranging from 0.2% to 3%.[1] Dislocations occurring early after surgery are common owing to inadequate capsular bag or ciliary sulcus support. Other risk factors of IOL dislocation include high myopia, trauma, pseudoexfoliation syndrome, uveitis, post-vitreoretinal surgery, and neodymium-doped yttrium aluminum garnet laser–induced capsulotomy.[1-3] The use of the three-piece IOL is often associated with intra-operative complications such as an unstable capsular bag, zonulysis, posterior capsular rupture, and capsulorhexis radial extension. The IOL is often placed into the sulcus or directly into the capsular bag, and this may result in postoperative IOL instability or dislocation.

Symptoms of dislocated IOL range from drop in visual acuity to diplopia. In cases of posteriorly dislocated IOL into the vitreous cavity, there are additional risks of retinal breaks, retinal detachment, vitreous hemorrhage, and chronic cystoid macula edema. Surgical approaches for IOL implantation in eyes with inadequate posterior capsule support include anterior chamber IOL, iris-fixated IOL, and

intrascleral-fixated IOL. Intrascleral-fixated IOL is preferred owing to its physiological location with less risk of corneal decompensation, iris chafing, or uveitis-glaucoma-hyphema syndrome.[4]

Intrascleral IOL fixation involves the use of sutures for anchorage and hence carries risks of suture breakage and conjunctival erosion. In 2017, Yamane et al proposed a sutureless double-needle flanged technique,[5,6] which has been widely used with promising results.[7-10] We reviewed a case series of refixation of dislocated three-piece IOL using the double needle flanged technique. This technique uses a small corneal incisional wound and thus achieves better intra-operative anterior chamber stability and less risk of endothelial damage, postoperative astigmatism, and intraocular bleeding.

Methods

Medical charts of six patients who underwent refixation of subluxed or posteriorly dislocated three-piece IOLs with inadequate sulcus support between January and December 2018 were retrospectively reviewed. All surgeries were performed using the Yamane flanged technique by a single surgeon at Grantham Hospital Eye Center in Hong Kong. Rescuing of the dislocated IOL was attempted in all cases. The time from initial IOL implantation to IOL refixation, logMAR best-corrected visual acuity at baseline and months 1, 3, and 6, spherical equivalent at month 6, IOL horizontal and vertical tilt at month 6, and complications were documented. IOL tilt was calculated from horizontal and vertical images. A straight line passing through the iris-corneal angles on each side was used as the reference line. The angle between the reference line and the horizontal/vertical axis of the IOL was measured as the IOL horizontal/vertical tilt. The mean IOL tilt was defined as the mean measurement of horizontal and vertical tilts.[5] Statistic analysis was performed using the Graphpad (Prism8 v8.2.1). One-way ANOVA was used to compare repeated measurements at follow-ups.

Under general anesthesia, a 25-gauge vitrectomy was performed. The dislocated lens was retrieved into the anterior chamber using the Alcon 25-gauge intraocular serrated forceps (**Figure a**) Two small corneal paracentesis were created at 2 and 10 o'clock positions. While the dislocated lens was in the anterior chamber, capsular remnants were removed to free residual adhesions using 25-gauge curved scissors. Externalization of IOL haptics through the paracentesis wound may be necessary in cases with strongly adhered capsular remnants to facilitate its removal (**Figure b**). A 27-gauge bent needle was inserted through the conjunctiva at 1.5 mm from the limbus, with the scleral entry of needle head kept at 20° and an intrascleral tunnel of 1.5 mm (**Figure c**). The leading haptic of the IOL was introduced, and one third of the haptic was advanced into the lumen of needle with the aid of intraocular forceps (**Figure d**). Another 27-gauge needle was inserted 180° from and in the opposite direction of the first needle. The trailing haptic was docked into the needle lumen in the same fashion as the leading haptic (Figure e). Both needles were withdrawn at the same time to externalize the haptics. Low temperature cautery was used to create terminal bulbs on the haptics and these flanged ends helped to fixate the intraocular lens (**Figure f**).

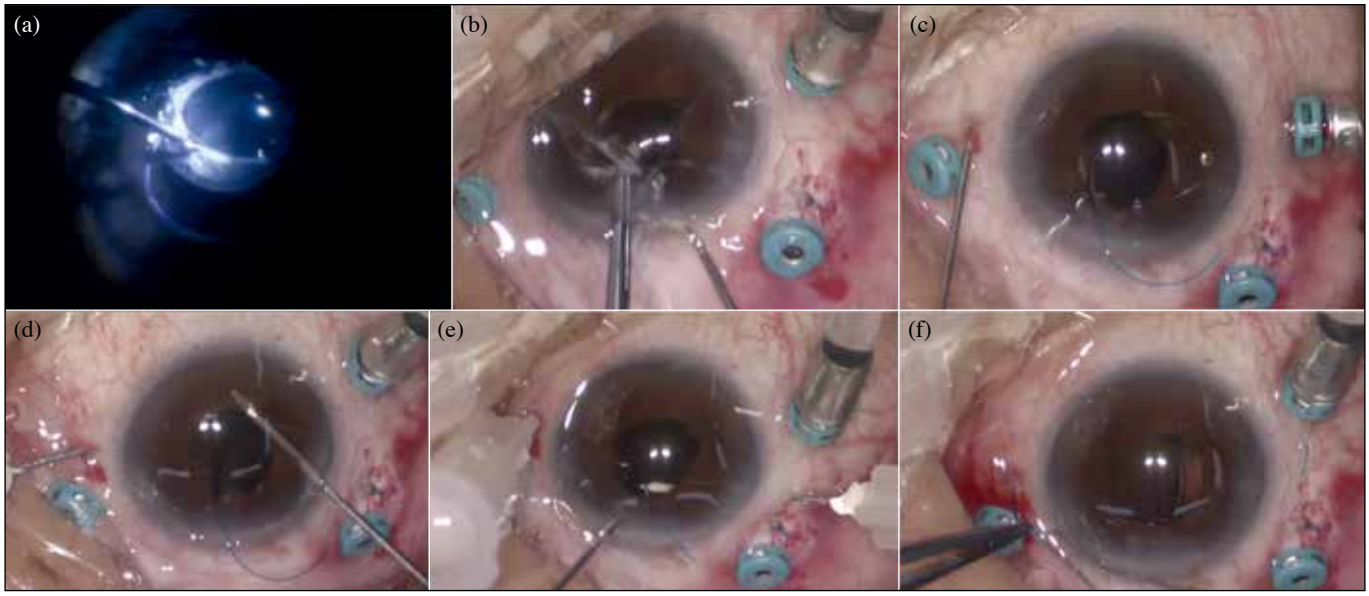

Figure. The double needle flanged technique: (a) The dislocated intraocular lens (IOL) is retrieved using an intraocular serrated forceps. (b) The IOL haptic is externalized via a paracentesis wound to facilitate removal of residual capsular remnants. (c) A 27-gauge bent needle was inserted. (d) The leading haptic of the IOL was introduced into the lumen of needle. (e) The trailing haptic is docked into the needle lumen in the same fashion as the leading haptic. (f) Both needles are withdrawn at the same time to externalize the haptics. Flanged ends are created with low temperature cautery.

Results

We reviewed six eyes in two men and four women (mean age, 71.17±5.565 years) who underwent refixation of subluxed (n=2) or dislocated (n=4) IOL caused by trauma (n=1), zonulysis following posterior capsular rupture (n=1), or unknown causes (n=4). The mean time from IOL implantation to IOL refixation was 12.6±9.7 years. Of the six cases, four had successful refixation of IOL including Sensar AR40e (n=1), Alcon MA60MA (n=1), and undocumented lenses (n=2). The two remaining cases had unsuccessful refixation of IOL and necessitated removal of the IOL and implantation of a new one. In one case with the Sensar AR40e, the haptic was broken at the optic haptic junction intra-operatively. In another case with the Hoya PY60R), the haptic was broken during docking manipulations. The two IOLs were placed into the anterior chamber and were cut into halves and removed via a 2.75-mm wound created by a corneal knife. A new three-piece (Sensar AR40e) IOL was then injected into the anterior chamber and implanted using the double needle flange technique.

The mean logMAR best-corrected visual acuity improved from 1.48 preoperatively to 0.680 at month 1, 0.400 at month 3, and 0.320 at month 6 (**Table 1**). The visual acuity of one patient was disregarded owing to the absence of visual potential secondary to a macula off retinal detachment before original IOL implantation. The mean spherical equivalent at month 6 was -0.520. In the four cases with the original IOL, at month 6 the IOL horizontal tilt was 2.5°±4.5° and the vertical tilt was -4.00°±2.754°. Comparing the four cases with the original IOL and the two cases with new IOL, there was no significant difference at month 6 in terms of visual acuity and IOL horizontal and vertical tilt. However, those with the original IOL had better spherical equivalence (-0.3438 vs -0.8759, p=0.018, **Table 2**).

One case developed Irvine Gass syndrome, which was resolved after topical non-steroidal anti-inflammatory drugs use. There were no major complications such as retinal detachment, choroidal detachment, suprachoroidal hemorrhage, endophthalmitis, and corneal decompensation.

Discussion

Scleral-fixating IOL is a popular procedure for secondary IOL implantation when there is instability in the capsular bag or anterior capsule. Conventionally, reimplantation of IOL requires a trans-scleral suturing technique. In 2017, Yamane et al introduced a sutureless double needle flanged IOL technique.[5,6] The IOL is fixed at exact centration and results in good axial stability and proper centration.[11] Such technique is relatively simple and minimally invasive, compared with the conventional procedure.

In cases of subluxed or dislocated IOL, the old IOL is often retrieved and a new IOL implanted. Retrieval of the subluxed or dislocated IOL requires a big corneal wound, resulting in delayed wound healing and postoperative astigmatism. The Yamane flanged technique enables saving of the IOL, faster

Table 1. Clinical characteristics of the six patients

Patient no.	Age, y	Time from initial intraocular lens implantation to refixation, y	LogMAR visual acuity				Replacement of intraocular lens	Spherical equivalence at month 6
			Baseline	Month 1	Month 3	Month 6		
1	63	13.5	HM	HM	HM	HM	No	-0.50
2	70	18	2.3	0.7	0.4	0.4	Yes	-1.00
3	79	8	1.0	0.5	0.5	0.5	No	-0.25
4	75	0.08	1.9	0.5	0.3	0.2	No	-0.375
5	72	28	1.9	1	0.5	0.3	No	-0.25
6	68	8	0.3	0.7	0.3	0.2	Yes	-0.75
Mean±SD	71.17±5.565	12.6±9.7	1.48±0.814	0.680±0.205	0.400±0.100	0.320±0.130	-	-0.520±0.300

Table 2. Comparison of cases with original versus new intraocular lens in terms of outcome at month 6

Outcome at month 6	Cases with original IOL (n=4)	Cases with new IOL (n=2)	P value
LogMAR visual acuity	0.3333	0.3000	0.8223
Spherical equivalence	-0.3438	-0.8750	0.018
Intraocular lens tilt (horizontal)	92.50°	88.50°	0.4879
Intraocular lens tilt (vertical)	86.00°	90.50°	0.0565

recovery, and a more stable anterior chamber. A similar flanged technique for dislocated IOL was reported to achieve good visual outcome of 20/25 without surgical complications in a 78-year-old patient.[9] The IOL was dislocated a few days after cataract surgery and was retrieved soon after. In our series, the IOLs remained in the eye for >12 years on average.

In our series, the dislocated IOL was successfully refixated in four of six eyes. Marked improvement of best-corrected visual acuity was observed, especially at postoperative month 6. The mean spherical equivalent at month 6 was satisfactory (-0.52 D), which is within the acceptable range of -1.0 D to -1.5 D to achieve best uncorrected distance and near vision.[12] IOL tilt is an important factor in the success of the surgery. >7° of IOL tilt significantly decreases visual acuity.[13] In our series, the mean IOL tilt of 2.5°±4.5° horizontally and -4.00°±2.754° vertically is within the limits to avoid visual disturbances. The two patients with replacement of IOL had a poorer spherical equivalence, probably because of the use of a new IOL, the presence of larger (2.75 mm) corneal incision, and the manipulation of IOL explantation. Nonetheless, studies with a larger sample size are needed to reveal group differences more accurately.

The existing three-piece IOLs had more angulated haptics owing to prolonged implantation within the capsular bag, compared with the brand new three-piece IOLs. In the two cases with replacement of IOL, the haptics were broken while being angulated to fit into the 27-gauge needle. Careful intra-operative assessment is crucial for haptic-optic junction stability (to minimize dislocation at the junction), haptic symmetry or bend (to minimize IOL tilt after implant), and haptic damage or kink (to minimize breakage during docking). When the angulation is too great, it is advisable to explant the old IOL and to replace it with a new one, as the chance of a broken haptic during or after fixation is high. When the old IOL is kept, capsular remnants should be completely cleared, especially the fibrotic capsules that wrap around the haptics. This ensures smooth docking into smaller gauge needles such as a 30G thin wall or 27G needle. The Alcon 25G serrated forceps is useful in the capsular removal process and IOL retrieval as well as haptics guidance into the 27G needle for externalization. A pair of 25G curved scissors is used to dissect the fibrotic capsule or tissue. Capsular removal is performed within the vitreous cavity and in the anterior chamber; manipulation in the anterior chamber is easier owing to a superior view through the cornea. The double needle technique facilitates the second haptic docking. With the first needle/haptic rotated deep into the eye, the second haptic is more ergonomically aligned for docking with the needle. Nonetheless, with the old three-piece IOL, the angulation requires more rotation, which can be achieved with slightly less threading of the first haptic into the needle, leaving two-thirds exposed rather than one third. This enables the IOL to rotate further for easier docking with a bent haptic.

The decision to keep the existing IOL was made intra-operatively. It was not known whether the haptics of unknown IOLs could be threaded into the needles. The integrity of the optic-haptic junction was difficult to assess after manipulation. There was a risk of breakage during haptic externalization or after surgery. Each IOL was brought into the anterior chamber for inspection, and the haptics were externalized via the paracentesis wounds for removal of capsular remnants. This is a good opportunity to inspect and manipulate the haptics for instability. In the two cases with IOL replacement, the old IOL design and long duration of implantation may have played a role. The Hoya lens had very small round bulbs at the haptics that made docking difficult, but the optic-haptic junction seemed to be very strong. The Sensar lens had been implanted for >18 years, and the junction may have weakened. In addition, the patient had had bilateral recurrent uveitis since 2012, and the IOL material may have weakened. The IOL design, duration of implantation, and occurrence of uveitis are important for patient selection. Long-term studies with a larger sample size are warranted to confirm our results.

Conclusion

Using the Yamane flanged technique to refixate the dislocated IOL achieves good stability and spherical equivalent of the IOL. Intra-operative assessment of the IOL and correct angulation and manipulation of the haptics are crucial for the success of surgery.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflict of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster (reference: UW-20-078).

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POSITION PAPER

Recommendations of the treat-and-extend regimen for neovascular age-related macular degeneration: 2020 updates

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Abstract

Anti-vascular endothelial growth factor (anti-VEGF) treatment is the gold standard of care for neovascular age-related macular degeneration (nAMD). To strike a balance between treatment burden and vision improvement, a treat-and-extend (T&E) regimen is the preferred approach to administer anti-VEGF treatment.

To facilitate implementation of the T&E regimen for nAMD in Hong Kong, a panel of retinal experts, with the support of Bayer Healthcare, held an online meeting on 15 September 2020 to discuss the latest published evidence and clinical experiences regarding the suitability and safety of anti-VEGF agents in the T&E regimen, patient selection, retreatment criteria, considerations for treatment discontinuation, and barriers to implementing the T&E regimen.

Compared with the 2019 recommendations, this 2020 version contains several major updates including differentiation of fluid compartments in retreatment criteria, additional considerations for patient selection, streamlined criteria for treatment cessation, and applicability of the T&E regimen in patients with polypoidal choroidal vasculopathy (PCV).

These updated recommendations are expected to facilitate implementation of the T&E regimen for nAMD including PCV in Hong Kong, with the aims of improving patient visual acuity, lowering treatment burden, and facilitating service capacity planning over the long term.

Key words: *Macular degeneration; Retina; Subretinal fluid*

Introduction

Neovascular age-related macular degeneration (nAMD) develops when chronic degenerative and hypoxic retina releases cytokines including vascular endothelial growth factor (VEGF) and placental growth factor (PGF), which act on VEGF receptors-1 and -2 to trigger downstream effects such as inflammation, vascular leakage, and pathological neovascularization.[1] Current evidence suggests that choroidal ischemia may play a role in the pathogenesis of nAMD.[2] Age-related macular degeneration is the leading cause of legal blindness in adults aged >60 years, affecting around 196 million people worldwide.[3] In 2010, it was estimated that about 3000 new cases of nAMD develop in Hong Kong each year.[4] This number is expected to increase with an aging population.

The gold standard in nAMD management is intravitreal anti-VEGF injection, which used to be in a monthly fixed-dosing injection interval.[5-7] With the chronic progressive nature of nAMD, persistent monthly intravitreal injections pose a heavy treatment burden on both ophthalmologists and patients.[8] The PrONTO study was conducted to investigate an alternative reactive as-needed (pro re nata) regimen, in which injections are given in response to disease worsening based on regular monthly monitoring for predetermined visual acuity and/or anatomical criteria.[9] The results shed light on the possibility of lowering treatment burden.[9]

The subsequent SUSTAIN, CATT, and IVAN studies re-evaluated the pro re nata regimen but failed to replicate the positive outcomes of the PrONTO study.[10-12] In view of the mixed results, a proactive individualized treat-and-extend (T&E) regimen was proposed, with the aim of achieving similar visual acuity gain with fewer clinic visits, compared with regular monthly dosing.[13] The principle of the T&E regimen is to administer injections at individualized intervals based on visual acuity and/or anatomical response, with no monitoring visits required.[13]

Patients with nAMD require constant treatment to maintain vision outcomes, as treatment discontinuation is associated with lesion reactivation and visual acuity loss in the long term.[14,15] Maintenance of vision gains in treated patients is poor over time, and may be worsened with fewer anti-VEGF injections administered.[16] The pro re nata regimen is associated with undertreatment and poorer visual outcomes, compared with a fixed-dosing regimen.[17,18] To strike a balance between treatment burden and vision improvement, the T&E regimen requires fewer injections but with no signs of undertreatment (compared with a fixed-dosing regimen)[19-22] and improves visual outcomes with fewer clinic visits (compared with a pro re nata regimen).[23]

The T&E regimen allows for predictable and reduced numbers and frequency of clinic visits and facilitates service allocation (eg, arrangement of optical coherence tomography [OCT]) and reduces workload of healthcare professionals, particularly during the COVID-19 pandemic. At the same time, patients can receive more timely treatment, with the potential to reduce time for clinic visits and treatment cost in the long run, compared with a fixed-dosing regimen. Nonetheless, financial constraints, psychological unpreparedness, and fatigue from receiving a series of injections may refrain patients from choosing the T&E regimen. To facilitate implementation of the T&E regimen, clear recommendations on a treatment pathway with clinical and logistical details should be established.

On 15 September 2020, with the support of Bayer Healthcare, an expert panel of ophthalmologists from public, private, and academic institutions in Hong Kong held an online meeting to discuss the suitability and safety of anti-VEGF agents in the T&E regimen, retreatment criteria, surrogate markers for treatment decision-making, roles of fluid compartments, considerations for treatment discontinuation, and obstacles to the implementation of the T&E regimen. Based on the latest published evidence and expert opinions, the 2020 updated recommendations for practicing the T&E regimen for nAMD including polypoidal choroidal vasculopathy (PCV) was established, based on the recommendations in 2019.[24]

Recommendations

Logistics of a T&E clinic

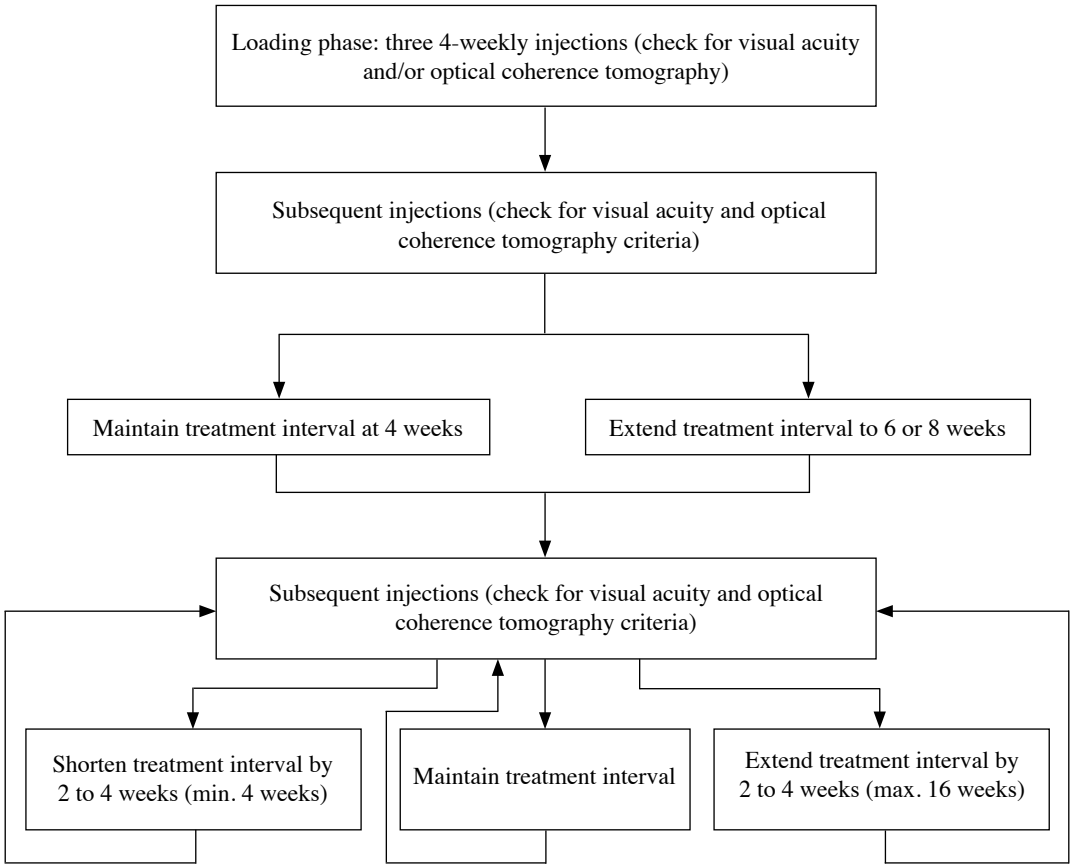
The logistics of a T&E clinic include: (1) checking for visual acuity, (2) performing an OCT test, (3) reviewing the patient condition by an ophthalmologist, (4) administering an injection, and (5) deciding on the next appointment for treatment, with the interval reduced, maintained, or extended.

Updates to previous recommendations

Items in the 2019 recommendations that are kept include the three initial monthly injections in the loading phase, the maximum injection interval of 16 weeks, and one of the criteria for extending the treatment interval (ie, no loss of ≥5 letters of the Early Treatment Diabetic Retinopathy Study [ETDRS]).

The T&E pathway is revised to illustrate more clearly whether to extend, maintain, or shorten the treatment interval as per visual acuity and anatomical criteria, which are modified based on the latest studies.[25,26] In particular, this update allows the possibility to extend the treatment interval with some tolerance of stable subretinal fluid (SRF) if there is ongoing anti-VEGF therapy. The minimum injection interval is changed from 4 weeks to 8 weeks, and treatment interval adjustment is recommended at 2-/4-week interval, instead of 1/2/4 weeks in the previous recommendation.[24]

Regarding considerations for treatment cessation, the previous recommendations suggested the need for 2 to 3 years of treatment and indefinite monitoring after treatment discontinuation.[24] The 2020 update recommends that treatment cessation can be considered in patients who are stable on anti-VEGF therapy every 16 weeks (q16w) for



Criteria for shortening (any of the following is met)	Criteria for maintenance	Criteria for extension (all of the following is met)
• Loss of ≥5 letters of Early Treatment Diabetic Retinopathy Study (ETDRS) or 1 Snellen line • New intraretinal fluid or subretinal fluid • Increased intraretinal fluid or subretinal fluid • Persistent intraretinal fluid • Residual subretinal fluid >200 μm • New macular hemorrhage • New neovascularization	• Residual but decreased intraretinal fluid • No loss of ≥5 ETDRS letters • Stable residual subretinal fluid ≤200 μm • No new macular hemorrhage • No new neovascularization	• No loss of ≥5 ETDRS letters (1 Snellen line) • Absence of intraretinal fluid • Stable residual subretinal fluid ≤200 μm • No new macular hemorrhage • No new neovascularization

Figure. Proposed treat-and-extend regimen using intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for the treatment of neovascular age-related macular degeneration and polypoidal choroidal vasculopathy.

1 year (ie, three injections), with 1-year post-cessation observation, which is in line with the recommendations by a UK expert panel.[27]

For patient selection, the 2020 update recommends that, in addition to single-eye patients, the T&E regimen should be considered in patients who have good visual acuity outcomes after three loading doses.

Three new sections are added. One discusses the relationships between molecular properties of an anti-VEGF agent and its duration of action, which is an important factor in choosing a suitable agent for use in the T&E regimen. Another new section reviews safety profiles of anti-VEGF agents based on data from clinical studies and post-marketing experience. The third new section explains the applicability of the T&E regimen in patients with PCV.

With respect to the limitations of the T&E regimen, the practical issues on the implementation of the regimen in routine clinical practice (including financial considerations, resource limitations, and patient psychology) are discussed, as are strategies to boost the acceptance of the T&E regimen among patients.

Loading phase

Consistent with the previous recommendations, the expert panel recommends using three monthly injections in the loading phase.[24] The first injection is preferably administered on the day of OCT assessment. In the two subsequent visits, visual acuity and clinical status should be assessed, and OCT may not be required, because imaging results are not expected to change the treatment plan during the loading phase. Refraining from OCT may help to reserve service capacity and reduce patients' waiting time.

Four to eight weeks after the last loading dose, another injection can be administered depending on the patients' clinical performance, based on the set of extension/maintenance/shortening criteria. Both visual acuity and OCT should be checked to determine the next treatment interval.

Extension of treatment interval

At every subsequent visit, both visual acuity and OCT should be checked to determine whether the treatment interval should be extended, maintained, or shortened. Intraretinal fluid (IRF), visual acuity (in terms of ETDRS letters), new onset of macular hemorrhage, and neovascularization are the criteria for guiding the treatment interval, based on evidence from the FLUID and ALTAIR trials.[25,26]

Compared with visual acuity, intraretinal fluid is a more important surrogate marker for treatment decision-making because accumulation of fluid often occurs before visual acuity loss. In post hoc analyses of the CATT, IVAN, HAWK, and HARRIER trials, higher fluctuation of central subfield thickness is associated with more losses in visual acuity.[11,12,28] However, most panelists note that greater overall fluid resolution does not directly translate to better visual outcomes in nAMD. They recognize the significance of differentiating fluid compartments and suggest that IRF, rather than SRF, has a direct impact on visual acuity outcomes. A completely dry retina may not be necessary in nAMD management because the presence of IRF is associated with worse visual acuity over time, and residual SRF appears to have neutral or even protective effects on visual outcomes.[11,25,29-31] Although the exact mechanism is unclear, the presence of SRF is hypothesized to reduce the risk of vision-threatening macular atrophy.[11] Nonetheless, eyes with residual SRF are still receiving ongoing anti-VEGF therapy, and treatment should be continued in nAMD eyes with SRF.

In the FLUID trial of ranibizumab,[25] a T&E regimen that tolerated an SRF of ≤200 μm yielded non-inferior visual acuity outcomes, with fewer injections, compared with the more aggressive T&E regimen, which did not tolerate SRF. In the ARIES study that examined the early-start and late-start T&E regimen arms with aflibercept also showed that a treatment interval extension in eyes with an SRF of ≤50 μm could maintain robust visual acuity gain, and thus a dry retina may not be necessary.[32] The expert panel recommends that residual SRF can be tolerated and allowable for extending the treatment interval in a T&E regimen, with the aim of reducing treatment burden. 45.45% of panelists preferred to adopt a threshold of residual SRF of ≤200 μm (whereas 36.36% preferred ≤100 μm and 18.18% preferred ≤50 μm), based on the FLUID trial that supports reducing injection numbers and the treatment burden for patients while maintaining visual acuity. Different from residual SRF, a new onset of or an increase in SRF can be a sign of disease recurrence, which warrants shortening the treatment interval. SRF tolerance is only applicable to a T&E regimen. In the pro re nata treatment, any fluid should be treated completely and should aim for complete dryness to prevent progressive damage.

In the ALTAIR study,[26] aflibercept T&E regimens with 2- and 4-week extensions yielded similar visual and anatomical outcomes. 66.7% of the panelists recommended extending the treatment interval by 2 weeks, which is a more conservative and appropriate approach because many Hong Kong patients on a T&E regimen have only one functional seeing eye based on the panelists' clinical experiences. The remaining panelists suggested extending by 4 weeks (16.7%) or depending on clinical judgment (16.7%). The panel recommends extending the treatment interval by 2 weeks (up to 16 weeks) when the following criteria are fulfilled as per OCT and visual acuity assessments: (1) no loss of ≥5 ETDRS letters (1 Snellen line), (2) no residual IRF, (3) stable residual SRF of ≤200 μm, (4) no new macular hemorrhage, and (5) no new neovascularization (as per OCT angiography).

Reduction of treatment interval

In patients without any signs of disease recurrence (ie, loss of ≥5 ETDRS letters, new IRF or SRF, increased IRF or SRF, persistent IRF, residual SRF >200 μm, new macular hemorrhage, or new neovascularization), the treatment interval should be shortened by 2 weeks (the minimum injection interval is 4 weeks). In line with previous recommendations, no treatment is required for intraretinal cysts secondary to chronic multiple injections, which tend to be small on serial OCT scans compared with the development of IRF. An increase in fluid associated with pigment epithelial detachment may not necessarily lead to shortening of the treatment interval but should be monitored carefully.

Maintenance criteria

In patients with residual but decreased IRF and no other signs of disease reactivation (ie, no loss of ≥5 ETDRS letters, residual SRF ≤200 μm, no new macular hemorrhage, and no new neovascularization), the treatment interval should not be extended but can be maintained.

Cessation of treatment

Anti-VEGF therapy is associated with atrophy development, but it remains uncertain whether treatment burden or duration are causes.[33-35] The expert panel recommends that treatment discontinuation should be considered in patients who are stable on 16-weekly anti-VEGF therapy

for 1 year (ie, three injections per year), with the aim to reduce treatment burden. In view of the risks of disease reactivation and vision loss with undertreatment,[36] patients, especially those with a single functional eye, should be observed prudently for disease stability for 1 year after treatment discontinuation. Before deciding on cessation of treatment, clinicians should have a thorough discussion with patients on the risk-benefit balance. If patients refuse to stop treatment or encounter disease recurrence, 16-weekly anti-VEGF treatment should be maintained or initiated.

Selection of patients

Consistent with previous recommendations, the expert panel recommends using a T&E regimen in single-eye patients. A T&E regimen should be considered in patients who have good visual acuity outcomes after three loading doses, whereas patients with anti-VEGF-refractory nAMD (stationary or increased intraretinal or subretinal exudation despite more than three consecutive injections) or at younger ages (eg <70 years) may not be prioritized to receive a T&E regimen, because of a lack of relevant evidence, given that the mean ages of participants in the FLUID and ALTAIR studies were 79 and 74 years, respectively.[25,26]

Choice of anti-VEGF agents

The expert panel recommends that anatomical efficacy, visual efficacy, durability of action, and safety are factors that affect the uptake of an anti-VEGF agent in clinical decision-making. With respect to both anatomical and visual efficacy of an anti-VEGF agent, the binding affinity, potency, and intravitreal half-life are considered important contributors, as are the roles of molecular size and molar dose, as all molecular properties are closely related. The intravitreal half-life of an agent is the major determinant of its durability of action, while other molecular properties also play certain roles.

In Hong Kong, current licensed anti-VEGF agents for nAMD include ranibizumab and aflibercept;[37] brolucizumab may be approved in future as it has been approved in the USA and several developed countries.[38] Aflibercept has distinct molecular properties. Compared with ranibizumab and brolucizumab, aflibercept has higher binding affinity,[39,40] potency,[41] and estimated intravitreal half-life,[42-44] contributing to a longer estimated VEGF suppression time (ie, 71 days).[45-48]

Safety of anti-VEGF agents

The most common adverse reactions with intravitreal anti-VEGF therapy include conjunctival hemorrhage, reduced visual acuity, eye pain, cataract, and increased intraocular pressure.[20,26] Rates of serious adverse events such as intraocular inflammation and endophthalmitis are consistently low across a series of phase III trials of both aflibercept and ranibizumab.[49] Around 30 million vials of aflibercept have been sold globally; rates of retinal artery occlusion and/or retinal vasculitis are very low.[50] Such serious adverse events are rarely reported (0.1%) in patients treated with ranibizumab.[51] Newer anti-VEGF agents such as abicipar pegol[52] and brolucizumab[53,54] might be associated with increased risks of intraocular inflammation, retinal artery occlusion, and retinal vasculitis. This indicates the heterogeneity in safety profiles among the drug class. Larger molecules with Fc fragments have a longer systemic half-life, which possibly leads to a lower serum VEGF concentration and higher risk of systemic adverse effects.[55] However, no data support a clinical correlation between the systemic half-life and the risk of VEGF-related adverse effects. A comprehensive review reported that rates of ocular and systemic adverse events with aflibercept were low and similar to those of the control arm.[56]

Applicability of a T&E regimen to PCV

PCV, a subtype of nAMD, is particularly common in Asians.[57] The expert panel recommends that PCV can be treated with the T&E regimen. In the PLANET phase IIIb/IV trial, aflibercept monotherapy was noninferior to aflibercept plus photodynamic therapy in terms of improvements in visual acuity at weeks 52 and 96.[58,59] The T&E regimens have similar efficacy for typical nAMD and PCV.[60,61] Clinical experiences have also demonstrated the efficacy and safety of T&E regimens of aflibercept in patients with PCV.[62-64]

Limitations of a T&E regimen

Because of manpower and resource limitations, most public hospitals in Hong Kong do not go directly for a T&E regimen after the loading phase. In clinical practice of most panelists, a T&E regimen is offered to as many patients with typical nAMD or PCV as possible, but only <30% of patients are actively treated with a T&E regimen, because of the inability to do the injection and follow-up visit on the same day and the high treatment cost. Most patients who are actively treated with a T&E regimen are eligible for free treatment (eg civil servants or participants of a Hospital Authority special program that targets low-income or single-eye patients). Non-adherence to a T&E regimen is due to financial constraints, fatigue, and psychological unpreparedness for chronic management.

Conclusion

We recommended a T&E regimen for nAMD including PCV based on the latest clinical evidence and shared experiences. Compared with the pro re nata approach, the T&E regimen is expected to improve visual acuity, lower treatment burden, and facilitate service capacity planning in the long run.

Contributors

All authors contributed to the concept/design, acquisition of data, analysis/interpretation of data, drafting of the manuscript, and critical revision for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflict of interest

Alvin Kwok has received lecture fees from Bayer and Novartis. Timothy Lai has received consultancy honoraria and lecture fees from AbbVie, Allergan, Bayer, Genentech, Heidelberg Engineering, Novartis Pharmaceuticals, Oculis, and Roche. Wai-Ching Lam has received consultancy honoraria and lecture fees from Alcon, Bayer, and Novartis. Raymond Wong has received lecture fees from Bayer and Novartis. Other authors have no conflicts of interest to disclose.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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REVIEW ARTICLE

Emerging treatments for dry age-related macular degeneration with geographic atrophy: a systematic review

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Abstract

We aim to summarize various emerging treatments for geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD). The PubMed database was searched using keywords: 'treatment' and 'geographic atrophy' or 'dry age-related macular degeneration' on 19 June 2021. Of 121 articles yielded, 20 relevant clinical studies that were of 'English language' and 'published within 10 years' were included. The emerging treatments of dry AMD with GA were categorized into complement inhibitors, diet and supplement, cell-based therapies, and pharmacological agents. Complement inhibitors (C3 inhibitor pegcetacoplan, complement factor D, and C5 inhibitors) can significantly reduce the GA lesion area growth, as can Mediterranean diet and α-lipoic acid. Cell-based therapies such as palucorel and biosynthetic retinal pigment epithelium monolayer delivery can minimize GA lesion area and improve the best-corrected visual acuity. Pharmacological agents such as fenretinide, ciliary neurotrophic growth factor, trimetazidine, and brimonidine have prominent effects on GA, but emixustat hydrochloride, tandospirone, and sirolimus lack such effects. The Age-Related Eye Disease Study formulation remains important in reducing the risk of progression of GA secondary to dry AMD. A thorough understanding of the emerging treatment of GA may enable more personalized treatment. Nonetheless, the safety and efficacy of the treatment ought to be tested in trials with larger sample size, longer duration, and optimized dosage.

Key words: Cell- and tissue-based therapy; Complement inactivating agents; Dietary supplements; Geographic atrophy; Macular degeneration

Introduction

Age-related macular degeneration (AMD) is a chronic progressive disease of the central retina and a major cause of visual impairment.[1] The prevalence of AMD in the United States population aged ≥40 years is 6.5%.[2] By 2040, AMD is estimated to affect 288 million people in the world.[3] Approximately 5% of patients with early AMD progress to a late stage, with an increase of up to 15% over the past 15 years.[4] Visual impairment is associated with unemployment, decreased self-support, activity limitation, and lower quality of life.[5]

AMD can progress to choroidal neovascularization (wet form) or geographic atrophy (GA) [late dry form], which causes severe vision loss. In dry AMD, retinal pigment epithelium (RPE) undergoes apoptosis, and amorphic

extracellular deposits (drusens) are formed between RPE and the Bruch membrane, leading to central scotomas and metamorphopsia. In the advanced stage, drusen regresses and hyperpigmentation occurs, resulting in GA.[6] On optical coherence tomography (OCT), GA is characterized by the atrophy of RPE, photoreceptors, choriocapillaris, and outer nuclear layer.[7]

Unlike neovascular AMD that can be treated with anti-vascular endothelial growth factor, dry AMD with GA secondary to RPE or photoreceptors damage cannot be reversible by current therapies.[8] Hence, smoking cessation and vitamin or nutritional supplements remain the main option to improve the prognosis of dry AMD.[9] The Age-Related Eye Disease Study 2 (AREDS2) showed that dietary supplements can lower the risk of the development of wet AMD but have no effects on reducing annual GA lesion area.[10] This prompts studies to develop novel strategies to minimize GA lesions in patients with dry AMD and to reduce visual morbidity.

We aim to systematically review clinical studies published within 10 years about emerging treatments of GA secondary to dry AMD and their effectiveness in preserving vision. We categorized the treatments into complement inhibitors, diet and supplement, cell-based therapies, and pharmacological agents. The efficacy, safety profile, and limitations of various therapies are discussed and compared.

Methods

The PubMed database was searched on 19 June 2021 using keywords: 'treatment' and 'geographic atrophy' or 'dry age-related macular degeneration'. Only clinical trials and randomized controlled trials published within 10 years and written in English language were included. Of 121 articles identified, 20 clinical studies describing the novel therapies for dry AMD with GA were included. Review papers, meta-analyses, and case reports were excluded. The 20 studies were manually curated for subject relevance through abstract or full text by one author, followed by discussion on the relevance with another author who made the arbitration when there was disagreement on article selection (**Figure**).

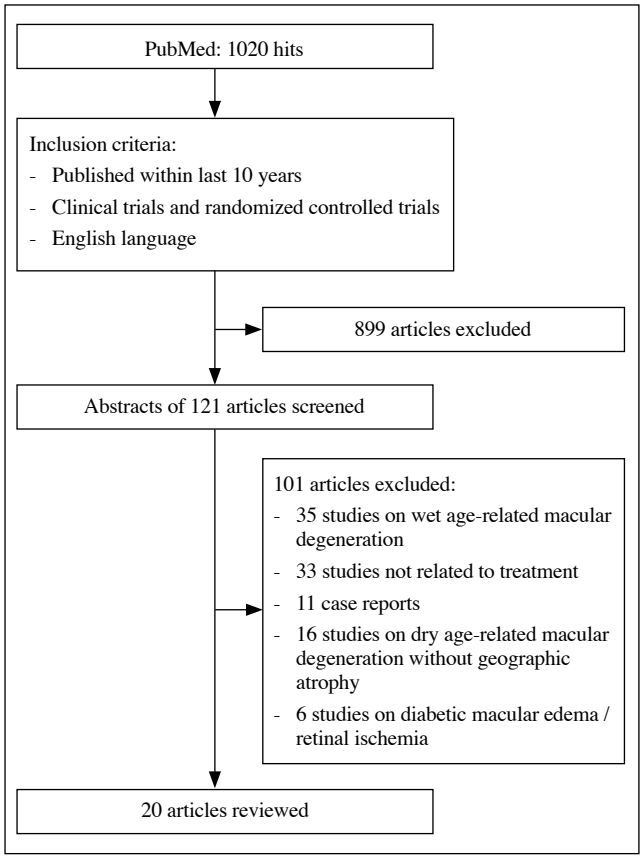

Figure. Flowchart of the PubMed database search strategy.

Results

The emerging treatments of dry AMD with GA were categorized into complement inhibitors (**Table 1**), diet and supplement (**Table 2**), cell-based therapies (**Table 3**), and pharmacological agents (**Table 4**).

Complement inhibitors

Complements are believed to partake in retinal degeneration secondary to AMD. Preclinical studies showed that complement is deposited in the eyes of patients with AMD.[11] C3 inhibitor pegcetacoplan, complement factor D inhibitor (lampalizumab), and C5 inhibitor were reported to improve the prognosis of dry AMD with GA.

C3 inhibitor pegcetacoplan

Complement C3 is the central component of the classical, alternative, and lectin complement activation pathway, which contributes to both innate and adaptive immunity.[12] Complement activation products have been shown to deposit drusens in dry AMD eyes.[13] In a phase 2 trial of 246 patients with GA secondary to AMD who were randomized to receive 15 mg pegcetacoplan intravitreal injection monthly, every other month, or sham injection for 12 months and were followed up at months 15 and 18,[14] at month 12, the increase in square root GA area growth was 29% smaller in the monthly pegcetacoplan injection group than the sham group (p=0.008), whereas the increase was 20% smaller in the every other month group than the sham group (p=0.067). Moreover, untransformed GA lesion reduced 20% and 30% in the every other month and monthly groups, respectively, with the effect most significant between months 6 and 12. Upon cessation of pegcetacoplan injection, the GA lesion growth rate showed no decline tendency. This reflects that pegcetacoplan is effective in slowing down the development of GA. However, pegcetacoplan had no prominent effect on the best-corrected visual acuity (BCVA) or foveal encroachment (the distance of GA from the fovea), compared with sham treatment.

Table 1. Studies of complement inhibitors for dry age-related macular degeneration (AMD) with geographic atrophy (GA)

Study	Groups and sample size	Parameters	Main results
C3 Inhibitor pegcetacoplan			
Liao et al,[14] 2020	246 patients allocated in a ratio of 2:2:1:1, with intravitreal injection of 15 mg pegcetacoplan every month or every other month, or sham injection monthly or every other month for 12 months; followed up at months 15 and 18.	Square root of GA lesion area, untransformed GA lesion, foveal encroachment, best-corrected visual acuity	Monthly and every other month pegcetacoplan injection reduced an increase in square root GA lesion area growth by 29% and 20%, respectively
Lampalizumab			
Holz et al,[17] 2018	906 patients assigned into a ratio of 2:1:2:1, with 10 mg intravitreal lampalizumab every 4 weeks, sham every 4 weeks, lampalizumab every 6 weeks, and sham every 6 weeks; assessed for 96 weeks.	Mean change in GA lesion, complement factor I-profile genetic biomarker, best-corrected visual acuity	Mean GA lesion increased from 1.93 to 2.09 mm^2 in all groups, with no significant benefit comparing lampalizumb and sham for profile biomarker.
Yaspan et al,[16] 2017	129 patients randomized into a ratio of 2:1:2:1 with 10 mg intravitreal lampalizumab monthly, sham monthly, lampalizumab every other month, and sham every other month; followed up for 18 months.	Mean change of GA area from baseline to month 18 using fundus autofluorescence, colour fundus photography, mean change in best-corrected visual acuity	Adjusted mean change of GA area at month 18 was 2.9 mm^2 in sham group, 2.3 mm^2 in monthly lampalizumab group; reduction in GA area growth was 0.6 mm^2 for monthly lampalizumab group and -0.2 mm^2 for lampalizumab every other month group.
Heier et al,[18] 2020	1881 patients randomized into a ratio of 2:1:2:1 with 10 mg intravitreal lampalizumab every 4 weeks, sham every 4 weeks, lampalizumab every 6 weeks, and sham every 6 weeks; followed up for 96 weeks.	Fundus autofluorescence measuring the GA lesion area, best-corrected visual acuity, low-luminance visual acuity, reading speed assessment.	Patients with lampalizumab every 4 weeks and 6 weeks showed 2.055 and 2.054 mm^2 enlargement in GA lesion area from baseline, respectively.
Eculizumab			
Yehoshua et al,[20] 2014	30 patients received intravenous eculizumab, 600 mg weekly for 4 weeks followed by 900 mg for 2 weeks; 900 mg weekly for 4 weeks followed by 1200 mg for 2 weeks, or placebo for 6 months at a ratio of 2:1.	Square root GA area measurement, best-corrected visual acuity, low-luminance visual acuity.	Mean standard GA measurement was 2.55 mm and 2.02 mm in the placebo and eculizumab groups, respectively. GA growth occurred in both groups at week 26.
C5 Inhibitor avacincaptad pegol			
Jaffe et al,[22] 2021	286 patients were randomized into a ratio of 1:2:2 avacincaptad pegol 2 mg, avacincaptad pegol 4 mg, and sham; followed up for 12 months.	GA area measured by blue light fundus autofluorescence, best-corrected visual acuity	Reduction in the mean GA growth rate was 27.4% for the avacincaptad pegol 2 mg group and 27.8% for the avacincaptad pegol 4 mg group, compared with corresponding sham groups.

Table 2. Studies of diet and supplement for dry age-related macular degeneration (AMD) with geographic atrophy (GA)

Study	Groups and sample size	Parameters	Main results
Mediterranean diet			
Keenan et al,[25] 2020	4255 participants were assigned to placebo, antioxidants, zinc, or the combination. 3611 patients received either the above supplements or with the addition of lutein/zeaxanthin, DHA/EPA, or the combination for 5 years.	Progression to GA by fundus photograph grades, alternative Mediterranean diet index.	Higher adherence to Mediterranean diet, especially high fish intake, led to lowered risk of GA or late AMD development, with a dose dependent association.
α-lipoic acid			
Sun et al,[29] 2012	32 patients had oral administration of α-lipoic acid and 30 patients had oral placebo for 3 months; followed up for 3 months.	Serum malondialdehyde, superoxide dismutase.	Patients with α-lipoic acid showed lowered serum malondialdehyde and superoxide dismutase, compared with placebo group.

Table 3. Studies of cell-based therapies for dry age-related macular degeneration (AMD) with geographic atrophy (GA)

Study	Groups and sample size	Parameters	Main results
Human umbilical tissue-derived cells palucorel			
Heier et al,[34] 2020	21 patients received single subretinal administration of palucorecel via suprachorioidal approach; followed up for 2 years.	Best-corrected visual acuity, GA area, optical coherence tomography retinal lesion and central subfield thickness	No improvement in GA area. No significant change from baseline in square root of area of GA in intervention eyes compared with fellow eyes.
Ho et al,[33] 2017	Single dose of palucorecel was placed in the subretinal fluid bleb adjacent to the GA area in 35 patients for 12 months.	Changes in GA area, best-corrected visual acuity	>30% of participants had a gain of ≥10 letters in best-corrected visual acuity in intervention eyes. Total GA area increased in intervention eyes.
Biosynthetic retinal pigment epithelial monolayer			
Kashani et al,[36] 2020	20 patients had single subretinal injection of monolayer of human embryonic stem cell-derived retinal pigment epithelium; followed up to 365 days.	GA area via intraoperative video analysis	Median GA area at baseline was 13.8 mm, whereas median GA area left uncovered by the implant was 1.7 mm. 86.9% of the baseline GA area was covered by the implant. In 5 subjects, >90% of the GA area was covered.

Lampalizumab

Complement factor D, a serine protease, is a rate-limiting enzyme of the alternative complement pathway.[15] Lampalizumab, a monoclonal antibody against complement factor D, is a potential therapeutic target to intervene in the complement activity to reduce the development of GA. In a phase 2 clinical trial of 129 patients with GA secondary to AMD who were allocated to 10 mg intravitreal injection of lampalizumab monthly or every other month or sham injection for 18 months,[16] the least square mean change adjusted for baseline GA area reduced 0.6 mm^2 and -0.2 mm^2 in the monthly group and every other month group, respectively, compared with the corresponding sham groups. There was a 20% reduction in mean change of GA area progression in the monthly group (p=0.117). The mean change of BCVA in the sham group and the monthly group was -4.9 letters and -3.3 letters, respectively. This shows that lampalizumab is an effective and safe treatment for GA.

However, other studies showed no efficacy of lampalizumab in reducing the GA lesion area. In a study of 906 Chroma and 975 Spectri participants with bilateral GA who were assigned to receive intravitreal injection of 10 mg lampalizumab or sham every 4 weeks or every 6 weeks for 96 weeks,[17] at week 48, the GA lesion area did not significantly differ between the sham groups and the every 4 weeks group (p=0.80) or the every 6 weeks group (p=0.59). The mean BCVA letter loss was 5 letters. In addition, complement factor I profile biomarker, a confirmed AMD common risk loci, did not differ significantly across groups. Similarly, in a phase 3 study of 1881 patients who were randomized into intravitreal injection of 10 mg lampalizumab or sham every 4 weeks or every 6 weeks for 96 weeks,[18] all groups had around a 2 mm^2 enlargement in GA lesion area at week 48. There was no significant difference in the BCVA (p=0.94) or low-luminance visual acuity (p=0.49) between every 6 weeks group and sham group. Furthermore, binocular or monocular maximum reading speed decreased in all groups, with no significant difference between lampalizumab and sham injection groups.

C5 inhibitor

Eculizumab, a humanized monoclonal antibody derived from anti-human C5 antibody, is used to treat paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. It inhibits C5 and prevents the formation of membrane attack complex.[19] In a study of 30 patients with GA who received intravenous injection of eculizumab 600 mg for 4 weeks followed by 900 mg every 2 weeks (n=10), 900 mg for 4 weeks followed by 1200 mg every 2 weeks (n=10), or placebo (n=10) for 24 weeks,[20] the mean changes of GA did not differ significantly between the eculizumab and placebo groups (p=0.96), and the change in mean GA enlargement rate did not differ significantly between low-dose and high-dose groups (p=0.40). At week 26, the placebo group showed a higher Early Treatment Diabetic Retinopathy Study visual acuity than the eculizumab groups (p=0.019) but stopped at week 52 (p=0.43).

On the contrary, avacincaptad pegol, a pegylated RNA aptamer that prevents C5 cleavage, was shown to prevent C5a and C5b formation, thus inhibiting cell death and cell lysis.[21] In a phase 3 trial of 286 patients with GA who were randomized into intravitreal injection of avacincaptad pegol 2 mg or 4 mg or sham injection for 12 months,[22] the reduction in mean GA growth rate was 27.4% in the avacincaptad pegol 2 mg group and 27.8% in avacincaptad pegol 4 mg group, compared with the corresponding sham groups (p=0.0072 and p=0.0051, respectively). Nonetheless, intravitreal injection of avacincaptad pegol 2 mg or 4 mg did not affect the mean change in BCVA, compared with sham injection.

Table 4. Studies of pharmacological agents for dry age-related macular degeneration (AMD) with geographic atrophy (GA)

Study	Groups and sample size	Parameters	Main results
Emixustat hydrochloride			
Rosenfeld et al,[38] 2018	508 patients were assigned to 24 months of oral daily emixustat 2.5, 5, 10 mg or placebo at a ratio of 1:1:1:1.	Normal luminance best-corrected visual acuity, total GA area	The annual growth rate for the total area of GA in the study eyes was similar between different treatment groups. Mean changes of normal luminance best-corrected visual acuity showed no significant difference across treatment groups.
Tandospirone			
Jaffe et al,[42] 2015	768 patients allocated (1:1:1) to receive twice-daily AL-8309B ophthalmic eyedrop 1.0%, 1.75%, or vehicle; followed up for 36 months.	Best-corrected visual acuity, total GA lesion area	An increase in the mean lesion size was observed in both the AL-8309B and vehicle treatment groups and was similar. Best-corrected visual acuity did not reveal significant changes among patients who received AL-8309B compared with those with vehicle eye drop.
Fenretinide			
Mata et al,[45] 2013	246 patients were allocated (1:1:1) to receive placebo, 100 mg fenretinide and 300 mg fenretinide for 2 years.	Visual acuity, GA lesion growth rate, serum retinol-binding protein level	Patients with 300 mg fenretinide resulted in 0.33 mm^2 reduction in annual growth lesion rate, with retinol-binding protein level <2 mg/dL.
Sirolimus			
Petrou et al,[49] 2014	6 participants had one study eye with 2% sirolimus in PEG 400 and 4% ethanol every 2 months, followed up for 24 months.	GA area by colour fundus photography or fundus autofluorescence, best-corrected visual acuity, central retinal thickness by spectral-domain optical coherence tomography	Increase in square root GA area from baseline was not significant in the study eyes at months 6 and 12 compared with fellow eyes.
Wong et al,[50] 2013	8 patients with 2% sirolimus in PEG 400 and 4% ethanol subconjunctival injection every 3 months, followed up for 24 months.	GA area by colour fundus photography or fundus autofluorescence, best-corrected visual acuity, central retinal thickness by spectral-domain optical coherence tomography	No significant absolute increase or percentage increase or square root transformation of GA area in study eyes compared to fellow eyes.
Ciliary neurotrophic factor			
Zhang et al,[52] 2011	51 patients with GA received NT-501 implant injection of high or low dose, or sham treatment in one eye, for 12 months.	Best-corrected visual acuity, GA lesion by fundus photos, retinal thickness by optical coherence tomography	High- and low-dose ciliary neurotrophic factor groups had a greater total macular volume. Progression in GA area was 2.42 mm^2 in sham group, compared with 2.19 and 2.03 mm^2 in low-dose and high-dose groups, respectively.
Trimetazidine			
Cohen et al,[54] 2012	1086 AMD patients randomized into group of 35 mg trimetazidine tablets twice daily or placebo for 3 to 5 years.	Visual acuity, GA lesion area, and choroidal neovascularization by retinal angiography	GA lesion >1/3 disk diameters occurred in 15% in trimetazidine group and 17.5% in the placebo group. The incidence per 100 patient-years was 5.11 and 6.45, respectively.
Brimonidine			
Kuppermann et al,[57] 2021	113 patients with GA were grouped into Brimo DDS 132 μg, Brimo DDS 264 μg, and sham group, with follow up for 24 months.	Best-corrected visual acuity, mean GA lesion size, reading speed	The growth in GA lesion area was significantly reduced by 19% and 28% in Brimo DDS 132 μg and 264 μg, respectively, compared with the sham group. Brimo DDS treatment was effective in patients with baseline GA lesion ≥6 mm^2.

Diet and supplement

Mediterranean diet and α-lipoic acid were reported to slow down the progression of GA secondary to AMD.

Mediterranean diet

Mediterranean diet contains a high content of antioxidants and anti-inflammatory nutrients, including vegetables, fruits, nuts, and unsaturated fat.[23] It has health benefits of lowering the incidence of coronary heart diseases, neurodegenerative diseases, diabetes mellitus, and cancers.[24] In a retrospective analysis of two cohorts (AREDS and AREDS2),[25] 4255 AREDS participants were allocated to receive placebo,

antioxidants, zinc or a combination for 5 years, whereas 3611 AREDS2 patients received either AREDS supplements or an addition of lutein/zeaxanthin, docosahexaenoic acid plus eicosapentaenoic acid, or a combination for 5 years. The proportional hazard regression for GA was 0.80 (p=0.0002) in AREDS and 0.71 (p<0.0001) in AREDS2 for the combined cohort. A higher alternative Mediterranean diet index adherence resulted in a lower risk of GA and late AMD progression. In AREDS, a higher fish intake led to a decreased risk of developing GA and late AMD. Hazard ratios for higher fish intake were <1 for GA. These demonstrate that adherence to Mediterranean diet is protective against late AMD and GA progression.

α-lipoic acid

α-lipoic acid is an antioxidant that scavenges hydroxyl radicals and nitric oxide.[26] It protects against oxidative injury and hence reduces the progression of Alzheimer disease, diabetes mellitus, and Parkinson disease.[27] α-lipoic acid also protects RPE cells from oxidation-triggered mitochondrial dysfunction in vitro.[28] In a clinical trial of 62 patients with dry AMD who were allocated to oral 600 mg α-lipoic acid daily or oral placebo daily for 3 months,[29] no significant difference was found between the two groups in terms of total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein (p>0.05). However, serum superoxide dismutase increased significantly after α-lipoic acid intervention compared with the baseline level (p<0.01). Superoxide dismutase is an antioxidative enzyme that protects oxidation-induced apoptosis in mouse RPE.[30] This suggests that α-lipoic acid enhances the antioxidant system in slowing down the development of AMD. In addition, serum malondialdehyde slightly decreased in α-lipoic acid group; this may be attributed to the increase in serum superoxide dismutase activity.

Cell-based therapies

Dysfunction and degeneration of the RPE cells are the main pathogenesis of AMD. Cell-based treatments aim to synthesize a RPE layer to deliver cytokines and regenerate the retina.[31] Palucorel and biosynthetic RPE monolayer has been shown to reduce the worsening of GA in patients with dry AMD.

Human umbilical tissue–derived cells palucorel

Palucorel consists of human umbilical tissue-derived cells derived from extraembryonic mesoderm.[31] Unlike mesenchymal stem cells, human umbilical tissue–derived cells do not grow infinitely in culture or differentiate spontaneously in vitro or when transplanted in vivo.[32] In a phase 1/2b clinical trial of 35 patients with GA who had palucorel placed in the subretinal space with the creation of a subretinal bleb and were administrated with 27 or 50 μL of palucorel and were followed up for 12 months,[33] the median change in BCVA was 4.5 letters in the intervention eye and -0.5 letters in the fellow eye. >30% of participants had a gain of ≥10 letters in BCVA in the intervention eye, but the total GA area increased in the intervention eye. The mean change in the square root of GA area was 0.356 mm in the intervention eye and 0.336 mm in the fellow eye. This reflects that palucorel may improve the visual acuity in patients but may not reduce the lesion size of GA.

Similarly, in a phase 2b study of 21 patients with GA secondary to AMD who received 50 μL of palucorel to the subretinal site using a suprachoroidal approach and were followed up for 2 years,[34] at month 12, none achieved the BCVA responder criterion (baseline improvement by ≥15 letters), with a mean change in BCVA of -5.7 in the intervention eye. OCT showed no improvement in retinal lesion thickness or central subfield thickness. The median change of square root of GA area was 0.26 mm in the intervention and 0.27 mm in the fellow eyes. Therefore, palucorel shows no significant benefits in terms of BCVA and GA growth rate.

Biosynthetic retinal pigment epithelial monolayer

Injection of stem cell–derived RPE suspensions did not improve retinal function within the GA area.[35] Replacement of RPE using a biosynthetic polarized monolayer of RPE was therefore developed. In a phase 1/2a study, an implant named California Project to Cure Blindness Retinal Pigment Epithelium 1 was fabricated, consisting of synthetic parylene substrate and a monolayer of human embryonic stem cell-derived RPE.[36] 15 patients underwent macular separation and subretinal pocket formation, followed by insertion of the implant into the subretinal space for 1 year. GA area prominently decreased on post-implantation colour fundus photographs. The median GA area covered by the implant was 86.9%, with 10 patients having >66% coverage of the original GA area. The baseline GA size inversely correlated with the percentage of GA area covered by the implant (p=0.002). This reflects that the size of the implant (3.5 × 6.25 mm) is appropriate for various GA sizes. The implant inserted through targeted subretinal hydrodissection around the GA area may be a practicable means for patients with GA. This treatment can potentially improve patient vision outcomes, as the procedure does not involve unnecessary detachment of the peripheral retina.

Pharmacological agents

Emixustat hydrochloride, tandospirone, fenretinide, sirolimus, ciliary neurotrophic factor, trimetazidine, and brimonidine are novel pharmacological treatments that may play a role in reducing GA progression.

Emixustat hydrochloride

Emixustat is a molecule that hinders the action of a visual cycle isomerohydrolase, RPE65. RPE65 inhibits the mobilization of vitamin A, thus interfering the supply of 11-cis-retinal and reducing bisretinoids accumulation.[37] Bisretinoids formation led to RPE dysfunction and apoptosis, eventually resulting in GA formation. In a phase 2b/3 clinical trial of 968 patients with GA who were randomized to receive oral emixustat 2.5 mg, 5 mg or 10 mg or placebo for 24 months,[38] the mean change of total GA area was similar across treatment arms (p≥0.81). The adjusted mean of the total GA area was 1.69, 1.83, 1.84, 1.69 mm^2/year in the emixustat 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. The annual linear

growth of total GA area after square root transformation was similar in different groups (p≥0.94). The mean change of normal luminance-BCVA was similar across treatment groups (p≥0.05). The median change in normal luminance-BCVA ranged from -2.0 to -4.0 letters at month 24. Emixustat did not achieve its primary and secondary efficacy end-points including GA lesion growth reduction and normal luminance-BCVA.

Tandospirone

Tandospirone, a $5HT_{1A}$ receptor agonist, is mainly used to treat major depressive disorder and anxiety.[39] Tandospirone possesses neuroprotective effects after traumatic brain injury and brain ischemia.[40] A formulation of tandospirone (AL-8309B) was produced for ocular use in the management of GA. An in vivo study revealed that AL-8309B had functional and structural protective effects on RPE and photoceptors under photo-oxidative stress.[41] In the Geographic Atrophy Treatment Evaluation phase 3 trial, 772 patients with GA were randomized to receive ophthalmic solution AL-8309B 1.0% or 1.75% or a vehicle at a ratio of 1:1:1 and were followed up for 36 months,[42] the mean GA lesion size increased in the AL-8309B and vehicle groups, with no significant difference between groups. The annualized lesion growth rate was 1.73 mm^2, 1.76 mm^2, and 1.71 mm^2 in the AL-8309B 1.0%, AL-8309B 1.75%, and vehicle groups, respectively. Likewise, change in BCVA was comparable among those with AL-8309B and those with vehicle eye drops. Only 38% and 35% of eyes had BCVA of ≥10 letters after treatment of AL-8309B 1.0% and AL-8309B 1.75%, respectively. This shows that tandospirone lacks efficacy as an ophthalmic solution.

Fenretinide

Fenretinide, a synthetic product of vitamin A, is endowed with therapeutic effects on prevention of obesity, type 2 diabetes, and cancer tumours.[43] Fenretinide competes with retinol and binds to retinol-binding proteins. This helps slow down the formation of a cytotoxic compound, *N*-retinylidene-*N*-retinylethanolamine, which was deleterious on RPE.[44] In a phase 2 trial of 246 patients with GA who received 100 mg or 300 mg daily oral fenretinide or oral placebo for 2 years,[45] all patients had a loss of 10 to 11 letters in the visual acuity. Nevertheless, the median GA lesion growth rate decreased 0.33 mm^2/year in those with 300 mg fenretinide, compared with placebo group (p=0.1848). Patients with 100 mg fenretinide revealed a similar trend. This indicates that fenretinide is effective in reducing the growth of GA lesion in a dose-dependent manner. A reduced GA lesion area correlated with a reduced serum retinol binding protein level of <2 mg/dL (r^2=0.478). Hence, reduction in serum retinol binding protein may lead to smaller lesion growth of GA.

Sirolimus

Sirolimus is an long-term immunosuppressant commonly used after renal transplant.[46] It inhibits a kinase named mammalian target of rapamycin and leads to a change in cellular metabolism, growth, and survival.[47] Local sirolimus application have certain effects on ocular pathologies including diabetic macular edema, uveitis, and diabetic retinopathy.[48] In a phase 1/2 study of six participants with bilateral GA who received intravitreal injection of 2% of sirolimus for 24 months,[49] the mean absolute increase and square root increase in GA area did not differ significantly between the study eye and the fellow eye on colour fundus photography (p>0.05). Four participants resulted in more decrease in central retinal thickness in the study eye, with more retinal thinning in central retinal subfield thickness and macular volume. There was a greater loss of BCVA in the study eye than the fellow eye. These suggest that intravitreal sirolimus may not be safe or effective in managing GA lesions.

In a phase 1/ 2 study of eight patients with GA who received subconjunctival injection of sirolimus every 3 months for 24 months,[50] all study and fellow eyes showed an increase in total GA area and showed no significant difference in mean percentage increase and mean absolute increase (p=0.41). Using colour fundus photography, fundus autofluorescence or confocal scanning ophthalmoscopy, the square root transformation of GA area was similar results between study and fellow eyes. The mean BCVA dropped by 21 letters and 3 letters in the study and fellow eyes, respectively (p=0.03). The central subfield mean retinal thickness and macular volume decreased progressively in both eyes. This reflects that subconjunctival sirolimus may not be beneficial to minimize GA progression, with an adverse effect on BCVA.

Ciliary neurotrophic factor

Ciliary neurotrophic factor, a member of the interleukin-6 family, retards photoreceptor cell death in retinal degeneration. It promotes the survival and differentiation of retinal cells via acting on ciliary neurotrophic factor receptor and downstream signal transduction pathways.[51] In a phase 2 study of 51 patients with GA who received NT-501 implant injection, followed by high- or low-dose or sham delivery of ciliary neurotrophic factor by encapsulated cell technology in one eye for 12 months,[52] the total macular volume was greater in high- and low-dose groups than in the sham group (p<0.001), with the increase more significant in the high-dose group than in the low-dose group (p<0.05). The low-dose group and the sham group had a greater decline in BCVA, but the high-dose group had relatively stable BCVA. Ciliary neurotrophic factor tended to reduce GA lesion. Progression in GA area was 2.42 mm^2 in the sham group, compared with 2.19 mm^2 and 2.03 mm^2 in the low-dose and high-dose groups, respectively. Hence, ciliary neurotrophic factor may affect GA lesion via its effect on photoreceptors.

Trimetazidine

Trimetazidine is a fatty acid oxidation inhibitor used in cardiovascular medicine to treat angina, left ventricular dysfunction, and cardiac cell death associated with coronary revascularization procedures.[53] In a phase 3 trial of 1086 patients with AMD who were randomized to receive 35 mg trimetazidine tablets or placebo twice daily for 3 to 5 years,[54] GA lesion >1/3 disk diameters in central and/or intermediate field occurred in 15% of patients in the trimetazidine group but 17.5% of patients in the placebo group. The effect of trimetazidine was more favourable in those of male sex

(p=0.016), age <75 years (p=0.010), and presenting with isolated pigmentary changes (p=0.005). Respectively in the trimetazidine and placebo groups, the incidence per 100 patient-years was 5.11 and 6.45 (p=0.07), whereas the estimated 5-year cumulative incidence rate of GA was 30.78% and 37.94%.

Brimonidine

Brimonidine is an alpha 2 receptor agonist used to treat glaucoma and ocular hypertension.[55] It improves the survival of human RPE and Müller cells in vitro and survival of retinal ganglion cells in a rat model after optic nerve injury.[56] In a phase 2 study that used an intravitreal implant with brimonidine in a biodegradable polymer matrix named Brimo DSS,[57] 113 patients with GA were randomized to receive Brimo DDS 132 μg or 264 μg or sham treatment and were followed up for 24 months. At month 12, the mean change in GA lesion area in the study eye was 1.78 mm^2, 1.59 mm^2, and 2.19 mm^2, respectively. The growth in GA lesion area significantly reduced by 19% and 28% after Brimo DDS treatments (p=0.032 and p=0.028, respectively), compared with sham treatment. Brimo DDS treatment was effective in patients with baseline GA lesion ≥6 mm^2, with a consistent reduction in GA area in both treatment groups at months 3 and 12, compared with the sham group. However, there was no significant improvement or worsening in BCVA or reading speed in study or fellow eye across all groups.

Discussion

Dry AMD is a common cause of blindness, but there is no approved treatment to reverse the RPE cell loss during the formation of GA.[6] On the contrary, wet AMD can be effectively managed by intravitreal anti-vascular endothelial growth factor injection. For dry AMD, AREDS formulation remains the only option to reduce the risk of GA progression.[10] To minimize GA lesion progression, various novel treatments have been proposed and their safety and efficacy assessed. Some are beneficial to BCVA or low-luminance visual acuity and thus have a better visual prognosis in the long run.

For complement inhibitors, C3 inhibitor pegcetacoplan has shown to reduce the mean change in square root GA lesion area, whereas lampalizumab has shown to reduce GA lesion in one study[16] but not in others.[17,18] Such discrepancy could be due to selection bias and rigorous exclusion criteria that preclude patients with pre-existing conditions and hence result in a weaker representation of the general population in one study.[18] In another study, the duration of follow-up lasted only 48 weeks, and the exclusion and inclusion criteria did not take into account those with unilateral GA and those with GA secondary to causes apart from AMD or earlier disease stages.[17] The effect of C5 inhibitor on minimizing GA lesion area showed diverse results between studies. One study reported a prominent reduction in GA area after avacincaptad pegol injection; this may be due to the low dose of eculizumab used and the intravenous (rather than intravitreal) route of administration.[20] A systemic route might have hindered the direct delivery of eculizumab to RPE cells. Regarding the safety profile, although pegcetacoplan exerted no significant effect on intraocular pressure, three patients with monthly injection experienced endophthalmitis.[14] Endophthalmitis occurred in five of 1252 patients with intravitreal lamaplizumb injection.[17] This suggests the use of a liquid pegcetacoplan formulation without reconstitution to reduce the risk of infection after intravitreal injection.

Cell-based therapy using palucorel showed no significant improvement in GA area. Palucorel was reported to improve BCVA, but the total GA lesion increased after 1 year.[33] This may be due to the limited sample size of only 35 participants. Interventional bias may also affect the clinical response assessment because the trial was not masked. This may lead to an overestimation of treatment advantages.[58] Likewise, in a study using a suprachoroidal approach,[34] the small sample size of 21 participants and the lack of masking or randomization may limit the power of the study. In both studies, the fellow eyes were not matched to the intervention eyes for baseline GA lesion and BCVA.[34,58] Regarding safety of cell-based therapies, 17.1% of patients experienced retinal detachment and 37.1% of them had retinal perforations.[33] Hence, further refinement of the surgical delivery of the umbilical-tissue cells or other cell delivery technologies is required to minimize the risk of complications.

Pharmacological agents including fenretinide, ciliary neurotrophic factor, trimetazidine, and brimonidine were found to reduce GA growth, whereas emixustat hydrochloride, tandospirone, and sirolimus did not result in significant changes in GA lesion. Emixustat failed to treat GA is because emixustat only targets RPE65, the visual cycle enzyme, but not other aspects in the multifactorial pathogenesis of AMD.[59] Thus, further combination with agents involved in the pathway leading to AMD should be considered. In one study of tandospirone, a rat model with severe acute photo-oxidative stress was used,[41] and it may not mimic the GA pathogenesis in humans. The dosage and duration of AL-8309B administration may not be optimal and requires further trials. The two studies on sirolimus included only six or eight participants; this decreases the statistical power and increases the margin of error.[49,50] Initiation rather than progression of GA was postulated to be more related to the immune aetiology of GA and therefore immunosuppressants may not be effective at a later stage.[50] Emixustat was associated with delayed dark adaption and chromatopsia,[38] whereas brimonidine Brimo DSS injection led to conjunctival hemorrhage and hyperemia.[57] Further studies are warranted to confirm the safety of drug therapy.

One limitation to this review study is that only patients with GA were included. Patients with early-stage dry AMD presenting with drusen were excluded. Studies involving potential treatments that prevent progression of dry AMD into choroidal neovascularization were missed out. Nevertheless, we aim to review treatments for GA formation because there is no breakthrough for therapies targeting GA progression.

The GA lesion contributes to photoreceptor dysfunction and vision loss eventually.

Conclusion

Complement inhibitors, diet and supplement, cell-based therapies, and pharmacological agents may slow down the progression of GA in terms of mean change of GA lesion area and BCVA. Nonetheless, the safety and efficacy ought to be tested in further trials with larger sample size, longer duration, and optimized dosage. A thorough understanding of the emerging treatment and pathogenesis of dry AMD with GA may enable more personalized management of GA.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflict of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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REVIEW ARTICLE

Development of herbal molecules in treating autoimmune uveitis: a narrative review

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Abstract

Current treatments for autoimmune uveitis involve the use of corticosteroids topically, locally (including subconjunctival, subtenon, orbital floor, and intraoucular injection), and systemically to attenuate the T cell–mediated response by impairing cell trafficking and activation to the uvea and dampening cell response to ocular antigens. However, long-term local injection of corticosteroids may result in raised intraocular pressure, cataracts, and glaucoma. Systemic use of steroids may result in severe morbidity. Immunomodulatory agents and biologics can circumvent some of these issues but may result in other adverse effects. Herbal molecules are potentially useful in treatment of autoimmune uveitis. We review the literature about the pathogenesis of autoimmune uveitis and the mechanisms, efficacy, and safety of herbal molecules (curcumin, green tea, triptolide, caffeic acid phenethyl ester, total glucosides of peony, and Longdan Xiegan Tang) as a therapeutic option or supplement for autoimmune uveitis.

Key words: Caffeic acid phenethyl ester; Curcumin; Epigallocatechin gallate; Longdan Xiegan Tang; Peony root extract; Triptolide; Uveitis

Introduction

Uveitis is the inflammation of the uvea that includes the iris, ciliary body, and vascular choroid. The damage from inflammation may extend to the sclera, vitreous, retina, and optic nerve. Uveitis mainly affects individuals aged 20 to 50 years and results in 5% to 10% of visual impairment worldwide, up to 25% of legal blindness cases in the developing world, and 5% to 20% of such cases in developed countries.[1-4]

Uveitis is classified based on the predominant anatomic site of inflammation (**Table 1**), clinical course (acute [<3 months], chronic [>3 months], and recurrent), laterality, etiology (infectious, non-infectious), and histopathological grading (granulomatous, non-granulomatous).[5,6] These classifications have implications on the epidemiology, presentation, and management. Anterior uveitis is the most common (particularly the idiopathic form), followed by posterior uveitis, panuveitis, and intermediate uveitis.[3,7-9] Rarely, uveitis may occur secondary to drug treatment for infections.[10]

Autoimmune uveitis (AU) or non-infectious uveitis is caused by a specific autoimmune response to retinal self-antigens or is a part of systemic autoimmune syndrome.[11] 25% to 30% of uveitis cases are associated with a systemic autoimmune or autoinflammatory disease such as seronegative spondyloarthropathies (ankylosing spondylitis and psoriatic spondylitis).[2,12] Uveitis occurs in 20% to 40% of ankylosing spondylitis cases and 7% to 16% of psoriatic spondylitis cases.[13,14] Other systemic diseases with manifestation to uveitis include sarcoidosis, juvenile idiopathic arthritis, Behcet disease, and Vogt-Koyanagi-Harada disease.[6,15,16] Uveitis can also be caused by non-systemic diseases such as birdshot choroidopathy[17] or as a complication of Mooren ulcer.[18] In a Chinese population, idiopathic anterior uveitis, Vogt-Koyanagi-Harada disease, and Behcet disease are the most common etiologies for non-infectious uveitis.[8,19,20]

Table 1. The standardization of Uveitis Nomenclature Working Group classification for uveitis

Type of uveitis	Major site of inflammation	Subset
Anterior uveitis	Anterior chamber	Iritis (affecting the iris) Iridocyclitis (affecting the iris and ciliary body) Anterior cyclitis (affecting the ciliary body)
Intermediate uveitis	Vitreous	Hyalitis/vitritis (affecting the vitreous cavity and/or pars plana) Pars planitis (affecting the pars plana [obicularis ciliaris]) Posterior cyclitis
Posterior uveitis	Retina or choroid	Retinitis (affecting the retina) Choroiditis (affecting the choroid) Retinochoroiditis/chorioretinitis (affecting the choroid and retina) Neuroretinitis (affecting the optic disc)
Panuveitis	Anterior chamber and vitreous and retina or choroid	

Uveitis related to autoimmune disease is more common in developed countries; 70% to 90% of sight-threatening uveitis are reported to be non-infectious.[2,15]

Autoimmune uveitis in mouse models

The experimental AU mouse model is paramount in studying the pathogenesis of AU and efficacy of novel treatments.[11,21] AU is induced by peripheral immunization through injection of evolutionarily conserved retinal antigens such as retinal soluble antigen, interphotoreceptor retinoid-binding protein (IRBP), and immunogenic peptide fragments of IRBP such as K2 (consisting of IRBP residues 201-216)[22] and peptide 161-180 (used in the B10.RIII mouse strain).[23] These antigens are emulsified in complete Freund adjuvant (comprising mineral oil and heat-killed mycobacterium tuberculosis). Susceptibility to each antigen depends on the animal strain; some strains require additional immune stimulation with pertussis toxin.[24,25] Other methods of induction include adoptive transfer of uveitogen-specific lymphocytes and generation of transgenic mice that express IRBP-specific T cell receptors that spontaneously develop AU. The severity of AU can be assessed clinically (by fundoscopic examination) and histopathologically (by flow cytometry to assess severity and extent of inflammation, expression of cytokine and chemokine, and distribution of immune cells).[26,27] However, these methods of assessment have shortcomings.[28] Although fundus examination can assess retinal lesions and disease severity, it fails to determine cellular infiltration, retinal thickness, and visual function. Non-invasive methods are preferred so as to avoid disease progression secondary to excision. Optical coherence tomography enables real-time imaging of tissues in situ, revealing cellular infiltration, retinal thickness, and retinal lesions while correlating with fundus and histological grading. Electroretinography enables non-invasive and quantitative assessment of visual function and retinal response to light.

Pathogenesis of experimental autoimmune uveitis

A key player in pathogenesis of experimental AU is the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which regulates a multitude of genes that encode cytokines, chemokines, cell adhesion molecules, and molecules regulating cell survival. NF-κB has a complex role in initiation, propagation, and resolution of inflammatory responses.[29] NF-κB upregulates the expression of the pro-inflammatory cytokine such as tumor necrosis factor alpha (TNF-α), which is mainly produced by macrophages and neutrophils. TNF-α plays a pivotal role in inflammation and experimental AU leading to tissue destruction (mediated by macrophages) and inducing pro-inflammatory cytokines interleukin (IL)-1 and IL-6. TNF-α is highly expressed in experimental AU models.[30,31] NF-κB induces IL-12 and IL-23 expression from antigen-presenting cells that are essential in Th1 and Th17 polarization, respectively.[32] TNF-α is a potent activator of NF-κB and promotes inflammation via a positive feedback loop.[33] Neutralizing TNF-α activity dampens interferon-gamma (IFN-γ) production, macrophage activity, and retention, as well as improves clinical and histological scores in experimental AU models.[30] Targeting TNF-α is the basis for successful immunomodulatory treatments for AU. In patients with Behcet disease with uveitis, inhibition of TNF-α using infliximab prevents Th17 differentiation and reduces expression of pro-inflammatory cytokines IFN-γ, IL-6, and IL-17 in ocular fluids.[34] Therefore, NF-κB, TNF-α, IFN-γ, and pro-inflammatory cytokines such as IL-1, IL-6, and IL-17 are useful indicators for the efficacy of novel treatments in experimental AU models.

Th1 and Th17 cells are key to experimental AU models. The Th1 cells are induced by the cytokines IL-12 and IFN-γ. When activated, the Th1 cells produce both cytokines to orchestrate a cell-mediated (typically phagocyte-dependent) immune response.[35] Specifically, IL-12 signaling phosphoactivates the STAT4 transcription factor that induces IFN-γ production.[36] Aberrant activation of Th1 can lead to an autoimmune response and induce experimental AU.[37] However, IFN-γ has paradoxical effects on experimental AU induction and disease course. In the long term, exposure to IFN-γ exacerbates inflammation and damages retinal cells through potent activation of macrophages.[38,39] In recent studies, the paradigm has shifted to the Th17 cells in experimental AU pathophysiology.

Medical treatments for autoimmune uveitis

AU is primarily treated with corticosteroids; the administration route depends on the site of inflammation. Corticosteroids dampen the immune response by acting on intracellular glucocorticoid receptors to recruit deacetylases that transcriptionally silence proinflammatory genes.[40] In early disease stage, topical prednisolone acetate (1%) is usually used for anterior uveitis and localized periocular steroid injection (eg triamcinolone) for intermediate or posterior uveitis.[16] Adverse effects include raised intraocular pressure, cataracts, glaucoma, and ptosis secondary to repeated injections.[41] In cases resistant to initial treatment, immunosuppressive drugs such as methotrexate or cyclosporine are used. In experimental AU models, cyclosporine has shown to block calcineurin, which blocks the IL-2 signaling pathway to inhibit T cell development and prevent T cell differentiation into effector types.[42] However, high-dose, long-term systemic steroid use can lead to Cushing syndrome[20] and adverse effects in almost all organ systems. Immunomodulatory agents and biologics can circumvent some of these issues but may lead to other adverse effects. Biologic therapies involving TNF-α inhibitors such as adalimumab[43] and infliximab[44] are viable options.

Herbal treatments

Herbal compounds such as curcumin from turmeric (curcuma longa) and green tea extract (camellia sinensis) have ability to inhibit the disease process of AU. The effect of triptolide, caffeic acid phenethyl ester, total glucosides of peony, and Longdan Xiegan Tang on experimental AU has also been investigated (**Table 2**).

Curcumin

Curcumin is extracted from *Curcuma longa* (turmeric) and has been used for a wide array of purposes such as cosmetics, food conditioning, and medicine. Curcumin exhibits anti-inflammation and antioxidation properties by reducing proinflammatory factors and oxidative stress against ocular tissues. The mechanisms involve downregulating transcription factors and inflammatory mediators.[45] Curcumin possesses the capacity to eliminate oxidative stress from reactive oxygen and nitrogen species and activate

Table 2. Beneficial and harmful effects, anti-inflammatory mechanisms, and effect on inflammatory cytokines of curcumin, green tea extract/epigallocatechin gallate, triptolide, caffeic acid phenethyl ester, total glucosides of peony, and Longdan Xiegan Tang

Herbal compound	Beneficial effects	Harmful effects	Anti-inflammatory mechanisms	Effect on inflammatory cytokines
Curcumin	Anti-inflammation, antioxidation; curcuminoids: short-term AU symptomatic improvement, long-term relapses prevention; curcumin capsule: reducing the total number of patients with relapses and the number of episodes of relapses in individual patients; most sensitive toward patients with autoimmune uveitis	Gastric intolerance symptoms (0.8% of cases), diarrhea, nausea, rise in serum alkaline phosphatase and lactic dehydrogenase, dose-independent toxic effects (eg, headache, yellow stool)	Downregulating NF-κB, STAT proteins (eg, STAT-4), eliminating reactive oxygen species and reactive nitrogen species, activating endogenous antioxidant defense (eg, glutathione), and inhibiting gelatinase B expression	Downregulating IL-1, IL-2, IL-6, IL-12
Green tea extract/ epigallocat-echin gallate	Anti-inflammation and antioxidation, improvement in clinical manifestation and histopathological ocular damage by alleviating retinal-choroidal edema, retinal vasodilation, and visual impairment	Well-tolerated in healthy populations, no hepato-/nephro-toxicity; contraindicated in patients with renal failure or iron deficiency anemia	Downregulating NF-κB and 20S/26S proteasome complex, increasing Treg populations, and decreasing Th1 and Th17 populations	Downregulating IL-1β, IL-6, IL-12, IL-17A, IL-23, IFN-γ, and TNF-α; upregulating IL-10
Triptolide	Improvement in histopathological score (only before completion of T cell priming)	Not reported	Downregulating Th1-mediated inflammatory response, inhibiting K2-mediated lymphocyte proliferation (only before completion of T cell priming)	Downregulating IL-12, IFN-γ, and TNF-α
Caffeic acid phenethyl ester	Anti-inflammation, immunomodulation; histopathological improvement by reducing amount of focal linear lesion, severity of vasculitis, retinal fold, and inflammatory infiltrate; no detrimental effect on hematopoiesis or liver and renal functions	High affinity for albumin leading to herb-drug interactions	Downregulating NF-κB, inhibiting T cell proliferation	Downregulating IL-6, TNF-α, MIP-1β, and RANTES
Total glucosides of peony	Anti-inflammation, antioxidation, immunomodulation, and analgesic; improvement in clinical score (fundus examination)	Not reported	Downregulating MAPK, reducing CD4+, CD4+/CD8+, and IFN-γ, and increasing CD8+ cells	Downregulating IL-1β, IL-6, IL-17A, TNF-α, MCP-1, and RANTES
Longdan Xiegan Tang	Anti-inflammation, anti-allergy, and hepatoprotectant activities; histopathological improvement by reducing inflammatory infiltrate in anterior chamber and synechia of uvea disorder; a faster recovery rate	Increasing the risk of liver injury in patients infected with hepatitis B virus	Reducing CD4+/CD8+ cell ratio	Downregulating IL-17, IFN-γ, and TNF-α; upregulating IL-10

endogenous antioxidant defense including glutathione.[46] Curcumin inhibits gelatinase B expression and thus reduces angiogenesis in inflammation.[47]

In a study of corticosteroid use adjunct with curcuminoids (curcumin dietary supplement) for recurrent uveitis,[48] 122 patients with up to four relapses annually who had been followed up for 2 years were recruited for a 1-year observation. Curcuminoids was started once the patients had a new relapse. 15 patients were excluded owing to non-compliance. One patient developed gastric intolerance symptoms. In the remaining 106 (61 male and 45 female) patients who had relapses before intervention, only 19 had relapses after taking curcuminoids, which is an 80% decrease ($p<0.001$). 275 episodes of relapses were observed before intervention, but only 36 episodes were observed at the end of the intervention, which is an 87% decrease ($p<0.001$). Patients with recurrent AU were the most benefited from the intervention. Therefore, curcumin is considered a bioactive well-tolerated non-toxic therapy.

In a study of 32 patients with chronic anterior uveitis, 18 received curcumin alone (n=18) and 14 who had a reaction to paraphenylenediamine received curcumin in addition to antitubercular treatment.[49] Curcumin capsules were given three times a day and were followed up for 3 years. Outcome measures were symptomatic improvement and recurrence rate. After 2 weeks of intervention, 100% and 86% of patients in the respective groups showed symptomatic improvement. Over the 3-year follow-up, the recurrence rate was 55% and 36% in the respective groups. No patient developed any adverse effects. These results suggest that curcumin is useful in short-term symptom alleviation and long-term relapse prevention.

Curcumin has shown positive treatment efficacy in anterior segment eye diseases including conjunctivitis secondary to immunological responses.[50] However, in the perspective of chemistry and pharmacy, curcumin is considered a pan-assay interference compound and invalid metabolic panaceas, thereby leading to false treatment efficacy.[51] In addition, curcumin is not a good drug candidate owing to its poor pharmacokinetics and limited bioavailability. Nonetheless, curcumin has shown efficacy in clinical and in vivo studies (non-placebo- and placebo-controlled).[48,49,52] Therefore, advancement in knowledge today should not overthrow findings of previous curcumin studies.[52]

In a study of 25 patients with advanced pancreatic cancer who received 8 g of oral curcumin daily until disease progression, no treatment-related toxic effects were found in 24 patients despite extensive toxic monitoring including complete history taking, physical examination, blood tests (complete blood count, renal and liver function test), and diagnostic imaging.[53] In a study of 38 healthy individuals aged 40 to 60 years who received either 80 mg of curcumin daily or placebo for 4 weeks, curcumin resulted in lowering of plasma triglycerides and beta amyloid levels.[54] In contrast, in a study of 15 patients with advanced colorectal cancer who received curcumin 0.45 g to 3.6 g daily up to 4 months, two patients (who consumed 0.45 g and 0.9 g curcumin) had diarrhea after 1 and 4 months of treatment, respectively.[55] One patient (who consumed 0.9 g curcumin) experienced nausea, which resolved spontaneously. Four and three patients had a rise in serum alkaline phosphatase level and serum lactate dehydrogenase level, respectively. In a study of 24 healthy individuals who received escalation doses of 500 to 12000 mg curcumin, seven individuals experienced dose-independent toxic effects such as headache and yellow stool.[56] Therefore, toxicity of curcumin should be further investigated.

Green tea

Green tea is isolated from *Camellia sinensis*; its three main components namely caffeine, essential oils, and polyphenolic compounds such as catechins have beneficial health effects.[57] Green tea extract and its main component epigallocatechin gallate (EGCG) have shown favorable results in laboratory trials. EGCG alters naive $CD4^+$ T cell differentiation and slows down Th1 and Th17 differentiation and thus prevent the induction of IL-6.[58] Green tea extract has protective effect on intraocular infectious inflammation.[59]

In a murine study to investigate the effect of green tea extract and EGCG on intraocular autoimmune inflammation,[60] mice were randomly allocated into 12 groups, including different dosages of green tea extract and EGCG, dexamethasone (as positive control), and water (as negative control). Outcome measures were retinal-choroidal thickness, major retinal vessel diameter, and electroretinography amplitudes. Results suggested that green tea extract, but not EGCG alone, could be a potential anti-inflammatory agent against AU (**Table 2**). Less significant changes in EGCG-alone treatments may be because EGCG has poor pharmacokinetic properties or other components of green tea extract may play a role. Green tea extract and EGCG are likely to be well tolerated drugs in healthy populations.[60] There were no steroid-induced adverse effects such as hepatotoxicity or nephrotoxicity. Nonetheless, the presence of aluminum in green tea should be contraindicated in patients with renal failure, as a decrease in aluminum excretion may cause neurological symptoms.[57] The high affinity of green tea catechins for iron should be aware to prevent aggregation of symptoms in patients with iron deficiency anemia. In addition, green tea contains caffeine and may cause palpitations, which may be alleviated by extracting only the essence of green tea.

Triptolide

Triptolide (TRD) is a major active ingredient of *Tripterygium wilfordii* Hook F. It has shown lymphocyte proliferation and lymphocyte reaction inhibition effects on suppressing K2-induced experimental AU.[61] Mice with experimental AU were treated with phosphate buffer saline (control), cyclosporine (positive control), TRD–whole period (from days 0-28), or TRD–efferent period (from days 14-28) after immunization. Outcome measures were histopathological scoring of experimental AU, extent of lymphocyte proliferation, Th1-type cytokine mRNA expression, and percentage of apoptosis in $CD4^+$ T cells. Results showed

that the histopathological score was similar between the cyclosporine group and the TRD–whole period group. Both groups were able to inhibit K2-mediated lymphocyte proliferation and to decrease Th1-type cytokine mRNA expression (IFN-y, IL-12p40, TNF-α). However, the TRD–efferent period group developed AU. TRD has a cytotoxic effect on tumor cells of hematological malignancies. The percentage of apoptotic $CD4^+$ T cells between TRD-treated and -untreated groups was similar. This excludes the possibility of TRD-mediated cytotoxicity in which experimental AU is eliminated through Th1 cell apoptosis. Thus, TRD is only effective when the treatment is given before T-cell priming; it has a protective effect on experimental AU induction.

Caffeic acid phenethyl ester

A murine study investigated the effect of caffeic acid phenethyl ester (CAPE), a phenolic compound extracted from honeybee propolis, on AU.[62] CAPE was reported to have anti-inflammatory, and immunomodulatory properties.[63] The mechanism of CAPE was to specifically inhibit NF-κB activity by preventing its translocation into the nucleus.[64] CAPE alleviated the severity of AU in mice. Histological findings showed fewer focal linear lesions and milder vasculitis when CAPE was administered. Also, there was a reduction of retinal fold and less inflammatory infiltrate on the retina of CAPE-treated mice, compared with vehicle-treated mice. These results indicate that CAPE can suppress the ocular inflammatory response and preserve retinal structure in mice with AU. CAPE could reduce pro-inflammatory molecules. Flow cytometry showed lower levels of TNF-α, IL-6, and IFN-γ in CAPE-treated mice, compared with vehicle-treated mice. This is likely attributed to CAPE's effect on inhibiting the NF-κB pathway. CAPE-treated mice showed a significant decrease in the expression of MIP-1β and RANTES. MIP-1β is a potent chemoattractant of macrophages and T lymphocytes. RANTES aggravates the progression of endogenous posterior uveitis. IFN-γ can work synergistically with TNF-α to increase RANTES production by retinal pigment epithelial cells.[65] CAPE is incapable of suppressing T-cell proliferation. IRBP-specific T cells in the spleens and lymph nodes were evaluated; the proliferation rate of $CD4^+$ was similar between CAPE-treated and vehicle-treated groups. In terms of pharmacokinetics, CAPE has a strong ability to bind to human serum albumin by static quenching.[66] The CAPE-albumin complex can be a reservoir that can prolong its half-life and enhance bioavailability. However, this poses a risk of herb-drug interactions if the patient is taking other drugs that have high affinity for albumin, and the concentration of CAPE and other drugs will be unpredictable. The CAPE delivery system showed no sign of toxicity.[67] CAPE has no detrimental effect on hematopoiesis or liver and renal function. Hence, CAPE is a non-toxic copolymer.

Total glucosides of peony

A murine experiment investigated the effects of total glucosides of peony (TGP), which is extracted from the roots of *Paeonia lactiflora* Pall, on suppressing experimental AU.[68] TGP showed anti-inflammatory and immunomodulatory effects. Nine female C75BL/6 mice with or without experimental AU were randomly allocated into three groups: sham (no AU and no treatment), control (AU and saline treatment), and TGP (AU and TGP treatment). Outcome measures were clinical scoring of the fundus image, measurement of the concentration of inflammatory markers, flow cytometry, and western blot. Fundus measurements on days 14, 21, and 28 revealed a higher score in the control than TGP group. This indicates the ability of TGP in suppressing experimental AU–associated inflammation. The concentrations of proinflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines (MCP-1, RANTES), and Th17 cytokine IL-17A decreased in the intraocular fluid of the TGP group. Flow cytometry showed that TGP suppressed CD4+ and IFN-γ populations while increasing CD8+ populations. This finding is in line with other molecular studies that show that a decrease in Th1 cells alleviates symptoms of AU. Western blot analysis revealed a significant decrease in phosphorylation of p38, extracellular-activated kinase, and c-Jun-N-terminal kinase. This indicates the anti-inflammatory effect of TGP by suppressing the MAPK signaling pathway. Thus, TGP has remarkable results on autoimmune diseases such as rheumatoid arthritis. However, the finding of inhibition of both Th1 and Th2 cell function in suppressing AU contradicts with the traditional mechanism that only Th1 and Th17 cause intraocular inflammation.

Longdan Xiegan Tang

Longdan Xiegan Tang (LXT) is a mixture of 10 herbal extracts including Radix Gentianae, Radix Scutellariae, Fructus Gardeniae, Rhizoma Alismatis, Caulis Clematidis Armandii, Semen Plantaginis, Radix Angelicae Sinensis, Radix Rehmanniae, Radix Bupleuri, and Radix Glycyrrhizae. LXT has anti-inflammatory, anti-allergy, and hepatoprotectant activities. In a study of the effect of LXT on treating rats with experimental AU,[69] rats were divided into three groups: normal control (that received sterilized distilled water), experimental AU (via injection of IRBP1177-1191 emulsion), and LXT treatment (oral gavage of 200 mg/kg/day). LXT showed a high efficacy of alleviating symptoms of AU. LXT significantly reduced the inflammatory response of the anterior segment. Retinal camera and histological findings showed less severe fibrin exudate and obscured pupils after LXT treatment. Red reflex was detected in the LXT group but not in the experimental AU group. The LXT group had decreased inflammatory infiltration and fibrin exudation in anterior chamber, reduced synechia of the iris and ciliary body structure disorder, mild-to-moderate inflammation of the retina, and photoreceptor outer segment damage or lesions extending to the outer nuclear layer. The LXT group recovered at a faster rate than the experimental AU, particularly from days 14 to 18. Flow cytometry showed that the ratio of $CD4^+/CD8^+$ in lymph nodes and spleen reduced on days 12 and 16. This indicates a reduced immune response. However, there was no significant difference in $CD4^+$ and $CD8^+$ levels on days 12 and 16. Peak levels of IFN-γ, IL-17, and TNF-α pro-inflammatory cytokines were lower in the LXT group than the experimental AU group, particularly on days 8, 12, and 16. For IL-10, an anti-inflammatory cytokine,

was markedly elevated on days 12, 16, and 20. This indicates that LXT can suppress the inflammatory response by altering the production of different cytokines. In terms of safety, LXT contains Radix bupleuri that increases the risk of liver injury in patients infected with hepatitis B virus.[70] The harmful effect of LXT is correlated with the cumulative dose of Radix bupleuri. Bupleurum might be a source of hepatotoxicity.

Conclusion

Curcumin has potentials for treating AU. It improves symptoms and minimize relapses of AU. Green tea extract and EGCG have positive results in mice by reducing both clinical and histopathological scores and suppressing the relevant autoimmune T cell responses. They have anti-inflammatory activity and can dampen Th1 and Th17 responses. Nonetheless, patients at risk of iron deficiency anemia or renal failure are contraindicated. TRD, CAPE, TGP, and LXT may improve experimental AU by reducing inflammatory cytokine levels and minimizing clinical scores. TRD is effective only at the time of disease induction and therefore may not achieve similar efficacy in humans. AU is a complex disease with numerous underlying systemic pathologies. Exploring the potentials for a synergistic relationship between herbal drugs and current medical treatments may reduce the adverse effects of immunosuppression by reducing the dosages of corticosteroids.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflict of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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CASE REPORT

3T magnetic resonance imaging in management of orbital venolymphatic malformations: two case reports

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Abstract

Vascular malformations may occur during the development of the arterial, venous, and lymphatic systems in isolation or in combination. Orbital venolymphatic malformations (OVLM) are particularly challenging to treat because they infiltrate and remodel normal structures within the tight orbital space and lead to substantial ocular discomfort, visual disability, and facial disfigurement. Herein, we report two cases of OVLMs with different presenting clinical features and treatment options. We compare the image qualities among computed tomography and 1.5T and 3T magnetic resonance imaging and discuss how better anatomical resolution in the latter aid in the management of OVLM.

Key words: Congenital abnormalities; Magnetic resonance imaging

Case presentation

Patient 1

In March 2020, a 26-year-old Chinese woman presented to the accident and emergency department with a 5-day history of spontaneous right eye painful swelling and periorbital bruises. She had congenital right facial and parotid cystic hygroma. At age 3 to 5 years, she had undergone three debulking surgeries, which led to postoperative right facial nerve palsy. She also had four episodes of spontaneous retrobulbar hemorrhage that required hospital admissions at age 9, 11, 13, and 16 years. Each episode was preceded by upper respiratory tract infections and resolved after a course of oral antibiotics and steroids. Computed tomography (CT) of the orbit was performed during each episode.

On examination, her right eye had a 5-mm proptosis (baseline, 2 mm), near-complete ophthalmoplegia, and an intraocular pressure (IOP) of 48 mmHg. Best-corrected visual acuity was 20/30 without relative afferent papillary defect or optic disc swelling. Examination of the left eye was unremarkable. Urgent contrast CT of the orbits showed a homogenous soft tissue mass measuring 2.0×3.9×2.1 cm at the right retrobulbar intraconal region, which had increased in size compared with previous scans in 2014 (**Figure 1**). The mass appeared inseparable from the optic nerve and the medial and inferior recti and involved the right orbital apex and cavernous sinus. The orbital compartment syndrome resolved gradually after bed rest, anti-glaucomatous drops, and oral steroid. At 4 weeks after onset, 3T magnetic resonance imaging (Prisma Magnetom,

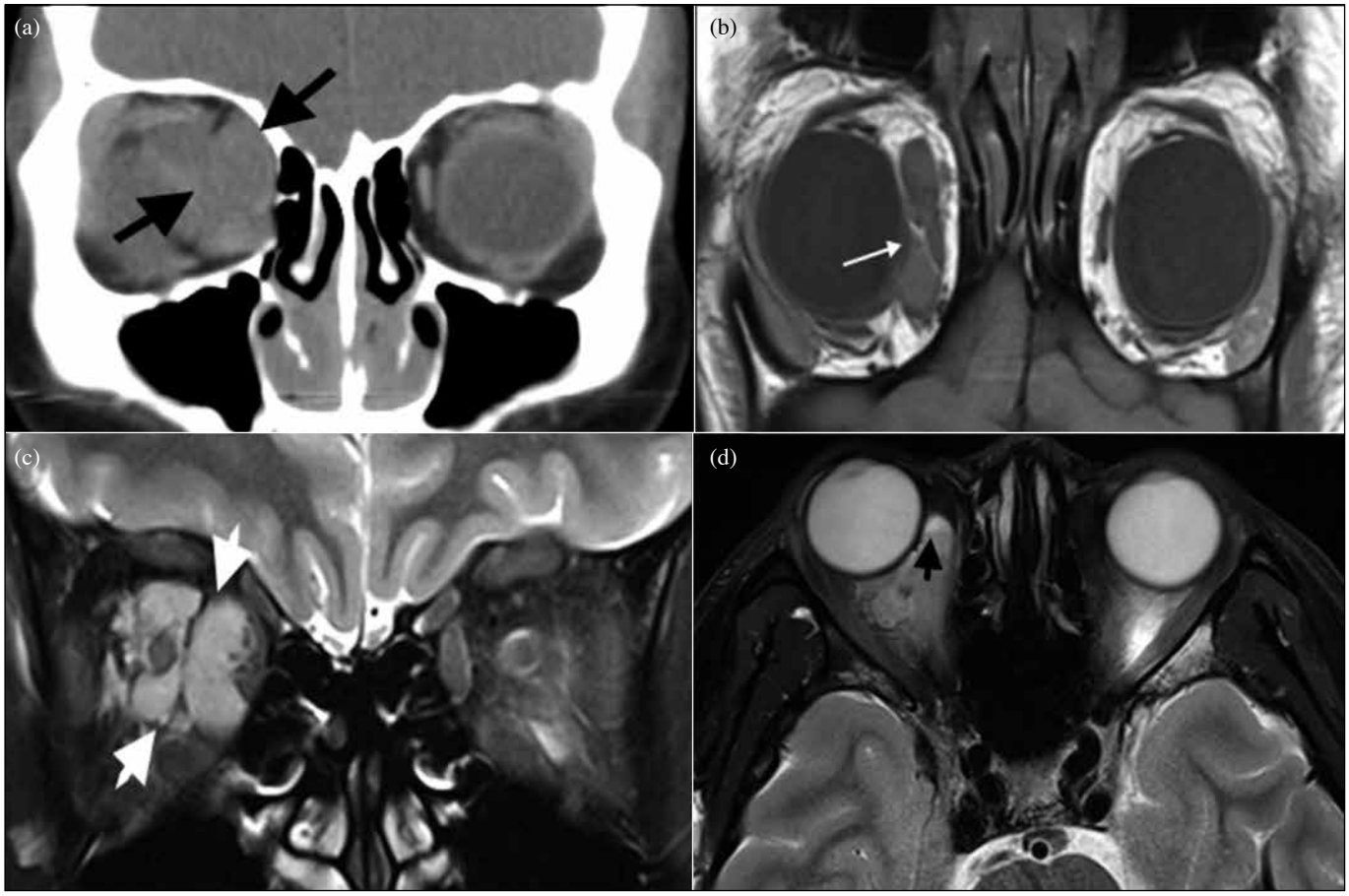

Figure 1. Patient 1: (a) Contrast computed tomography showing a soft tissue mass measuring 2.0×3.9×2.1 cm at the right retrobulbar intraconal region. (b) 3T coronal T1-weighted magnetic resonance imaging (MRI) at 4 weeks after onset of symptoms showing a multilobulated septated trans-spatial cystic lesion, slightly hyperintense to the extraocular muscle, occupying the right retrobulbar region. (c) Coronal T2-weighted MRI showing encasement of the optic nerve by the lesion and medial displacement of the medial rectus muscle. (d) Axial fat-suppressed T2-weighted MRI showing distinct fluid-fluid levels within the lesion suggestive of resolving intralesional hemorrhages.

Siemens Healthineers, Germany) showed a multi-lobulated septated cystic and venolymphatic malformation occupying almost the entire right retrobulbar region (**Figure 1**). The optic nerve was encased by the lesion and multiple intralesional fluid-fluid levels were present, suggestive of recent hemorrhages.

The patient was given treatment options of glue-assisted excision, sclerotherapy, combination of both, and oral Sirolimus. She opted for oral Sirolimus 1.5 mg daily.

Patient 2

In April 2018, a 30-year-old Chinese man presented with an enlarging purplish lesion in the medial canthus of the right eye, which increased in size with Valsalva maneuver and dependent posture. Physical examination showed a Valsalva-positive medial palpebral and caruncular conjunctival vascular lesion. His visual acuity was 20/18 in either eye with no diplopia or proptosis. Contrast CT of the orbits showed an enhancing soft tissue at the medial aspect of the right orbit, with the presence of phlebolith and bony remodeling, suggestive of long-standing communicating venous-dominant type of venolymphatic malformation (**Figure 2**).

Contrast 1.5T MRI performed elsewhere showed a poorly circumscribed, predominantly extraconal, transcompartmental mass measuring 13×21×17 mm suggestive of orbital communicating venous malformation (**Figure 2**). The lesion was T1-isointense to muscle and showed homogeneous contrast enhancement. 3T MRI showed multiple cystic components and fluid-fluid levels within the lesion, with better anatomically defined margins (**Figure 2**). The patient was given treatment options of glue-assisted excision or oral Sirolimus. He opted for glue-assisted excision.

Discussion

Vascular malformations may occur during the development of the arterial, venous, and lymphatic systems in isolation or in combination.[1] OVLMs are non-neoplastic congenital

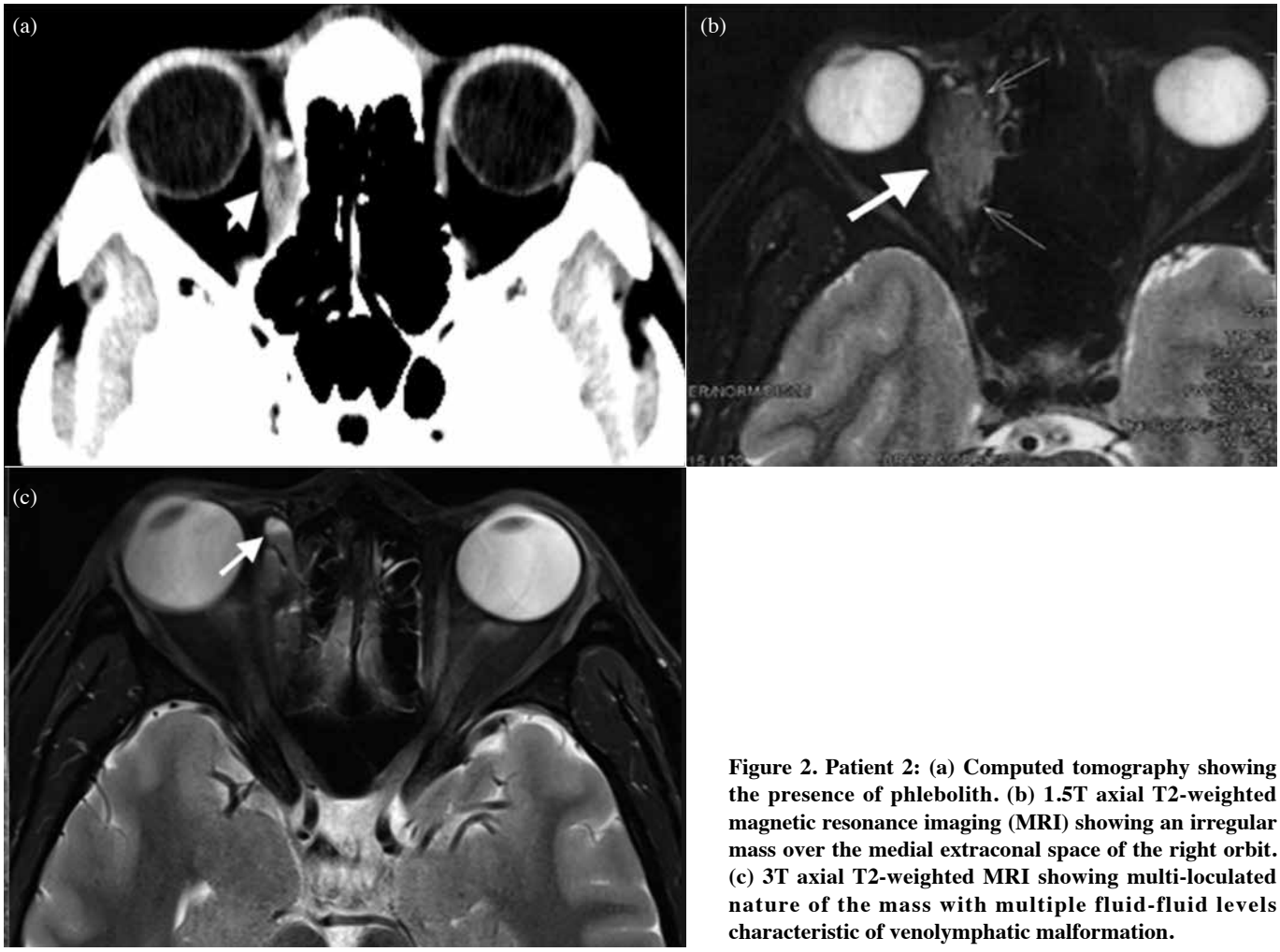

Figure 2. Patient 2: (a) Computed tomography showing the presence of phlebolith. (b) 1.5T axial T2-weighted magnetic resonance imaging (MRI) showing an irregular mass over the medial extraconal space of the right orbit. (c) 3T axial T2-weighted MRI showing multi-loculated nature of the mass with multiple fluid-fluid levels characteristic of venolymphatic malformation.

malformations and are classified into superficial, deep, combined (superficial and deep), and complex (orbital and extra-orbital) types according to their locations.[2] Clinical manifestations and management are based on hemodynamics and classified into no flow (type 1), low flow (type 2), and high flow (type 3). According to International Society for the Study of Vascular Anomalies, vascular malformation can be divided into high-flow (type 3) and low-flow (types 1 and 2) lesions. High-flow lesions include arteriovenous malformation and congenital arteriovenous fistula. Low-flow lesions include venous malformations, lymphatic malformations, and veno-lymphatic malformations.[3]

OVLMs are the most common low-flow orbital lesions and have mixed vascular elements histologically with different degrees of lymphatic versus venous components. Patients may present with proptosis, pain, limited extraocular movement, globe dystopia, and rarely loss of vision. Acute hemorrhage occurs after minor trauma or viral infections and may result in orbital compartment syndrome.

Imaging is crucial in the management of OVLMs in terms of location, nature, progression, and treatment. CT provides excellent details related to the bony anatomy, bony changes, and phleboliths, which may be seen in slow-flow lesions.[4] MRI is superior to CT in differentiating acute from chronic blood- or fluid-filled cysts and in providing anatomical details including loculation within the lesion and their relationship with the optic nerve, extraocular muscles, and cavernous sinus. Imaging quality of MRI depends on the magnetic field strength measured in Tesla (T), usually between 0.5 T and 3.0 T. With increasing tesla strength, the image quality increases and the time taken to perform the imaging decreases.[5] In 2002, the first 3T MRI scanner was approved for clinical use by the US Food and Drug Administration.[4] 3T MRI offers a higher signal-to-noise ratio than does the lower-field strength MRI, which leads to a higher spatial resolution constant.[5] At present, 1.5T short-bore MRI remains the standard technology in most hospitals. For head and neck, neural, musculoskeletal, and vascular imaging, 3T MRI has a stronger signal strength and higher spatial image resolution and is better at delineating anatomical details and tissue planes, compared with 1.5T MRI or CT. 3T MRI can also generate a higher contrast-to-noise ratio. This is particularly useful as orbital structures can be difficult to differentiate owing to their limited inherent contrast.[6] Valsalva maneuver on supine position may be performed during MRI when orbital varices are

suspected in order to determine the presence and the relative contribution of the distensible (communicating) component.

The management of OVLMs is challenging. The first-line treatment includes observation or simple aspiration of the anterior cystic components. Surgical debulking is difficult because of the poorly defined margin of vascular malformations, the risk of uncontrolled bleeding, the proximity to orbital structures, and the high recurrence risk related to incomplete excision. Recent development of therapeutic agents and advancements in MRI enable image-guided, individualized treatment of symptomatic lesions. From oral (sirolimus) to intralesional agents using sclerosants (bleomycin, doxycycline, sodium tetradecyl sulfate, alcohol) targeted for micro- and macrocystic lesions, liquid polymers (N-butyl cyanoacrylate glue) for venous components followed by controlled surgical debulking has evolved as a staged, multimodal approach for complex OVLMs. Although percutaneous sclerotherapy under sonographic and/or fluoroscopic guidance has been performed, complex lesions may benefit from additional orbitotomy exposure and intraoperative navigation guidance. Intermittent 3T MRI was recently used with 'in-and-out' technique to monitor MRI-compatible needle placement and sclerosant delivery during percutaneous treatment of venous malformation.[6]

Conclusion

3T MRI is superior to 1.5T MRI or CT in management of OVLMs.

Contributors

PTYW and KKLC designed the study. PTYW, KKLC, and WCWC acquired the data. PTYW, KKWC, and KKLC analyzed the data. PTYW drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflict of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatment and procedures and for publication.

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Announcement

The best original article award 2021 for fellows goes to Wong E, Chan A, Lam C, Lau W, Yam J, and Yu C for article titled *Retinoblastoma in Hong Kong from 2008 to 2019: looking back and moving forward* published in Hong Kong J Ophthalmol 2020;24:6-10.

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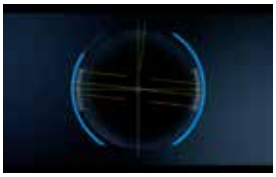

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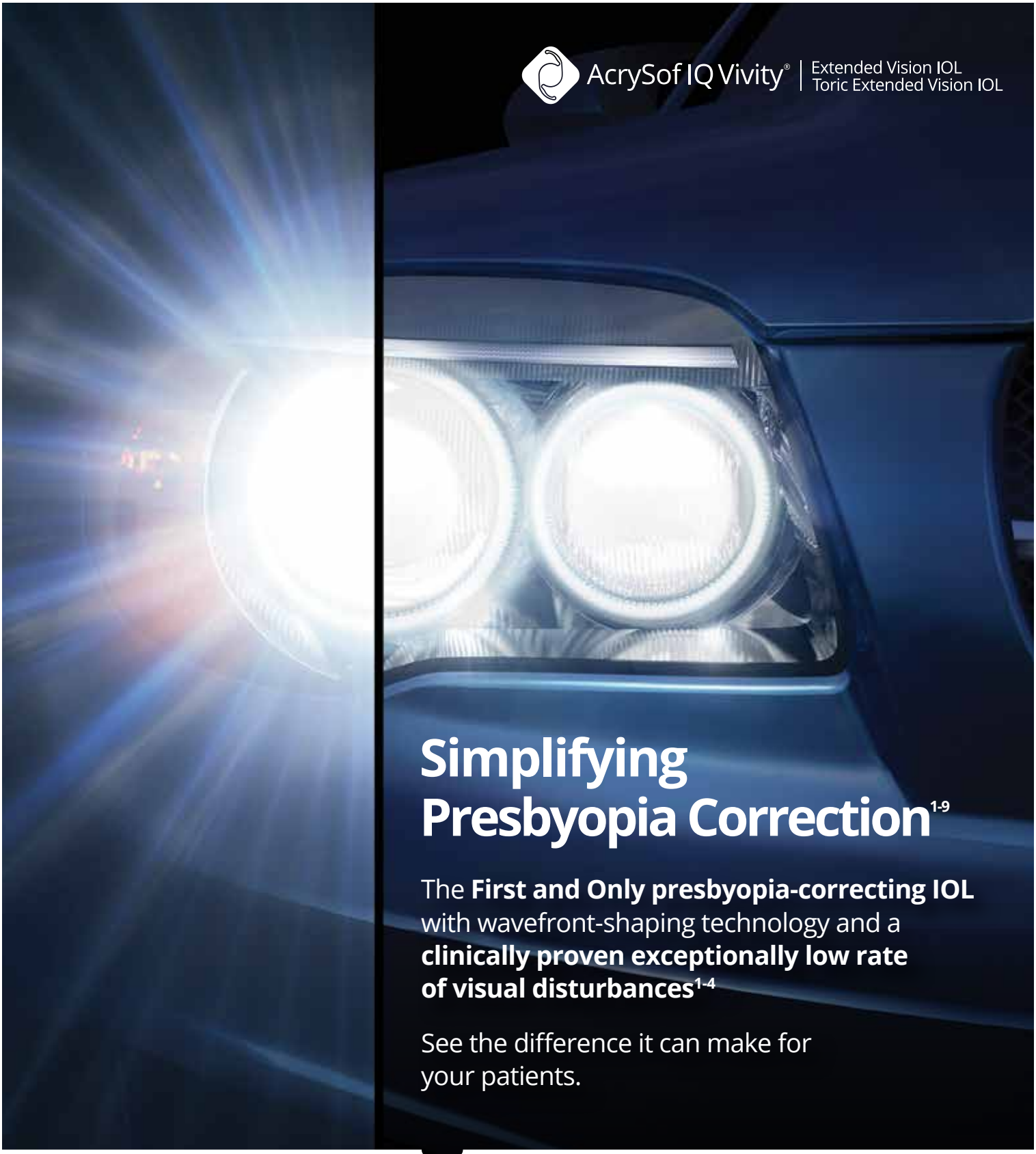

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In two head-to-head trials vs aflibercept, Beovu®[1]:

- Demonstrated **robust vision gains[2*]**
- Outperformed aflibercept in achieving **superior fluid resolution[1,2*†]**
- Maintained a **majority of patients on a q12w** interval immediately after loading through Week 48[1]
- Exhibited an overall **well-tolerated safety profile[3]**

INDICATION: Beovu® is indicated in adults for the treatment of neovascular (wet) age related macular degeneration (AMD)[1]

BEOVU® Important note: Before prescribing, consult full prescribing information. **Presentation:** Solution for injection. Each vial contains 27.6 mg of brolucizumab in 0.23 mL solution. Each pre-filled syringe contains 19.8 mg of brolucizumab in 0.165 mL solution. **Indications:** Beovu® is indicated in adults for the treatment of neovascular (wet) age related macular degeneration (AMD). **Dosage regimen and administration:** Single-use vial or single-use pre-filled syringe for intravitreal use only. Each vial or pre-filled syringe should only be used for the treatment of a single eye. Beovu® must be administered by a qualified ophthalmologist experienced in intravitreal injections. **Adults:** The recommended dose is 6 mg brolucizumab (0.05 ml solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. The physician may further individualise treatment intervals based on disease activity. If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Beovu® should be discontinued. **Special populations: ◆Renal impairment:** No dose adjustment is required. **◆Hepatic impairment:** No dose adjustment is required. **◆Geriatric patients:** No dose adjustment is required. **◆Pediatric patients:** Safety and efficacy have not been established. **Contraindications: ◆**Hypersensitivity to the active substance or to any of the excipients. **◆**Active or suspected ocular or periocular infection. **◆**Active intraocular inflammation. **Warnings and precautions: ◆Traceability:** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. **◆Endophthalmitis, intraocular inflammation, traumatic cataract, retinal detachment, retinal vasculitis, and/or retinal vascular occlusion:** Intravitreal injections, including those with Beovu®, have been associated with endophthalmitis, intraocular inflammation, traumatic cataract and retinal detachment. Proper aseptic injection techniques must always be used when administering Beovu. Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of Beovu®. In patients developing these events, treatment with Beovu® should be discontinued and the events should be promptly managed. Patients should be instructed to report any symptoms suggestive of the above mentioned events without delay. **◆Intraocular pressure increases:** Transient increases in intraocular pressure have been seen within 30 minutes of intravitreal injection with vascular endothelial growth factor (VEGF) inhibitors, including brolucizumab. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Beovu® while the intraocular pressure is ≥30 mmHg). Both intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. **◆Bilateral treatment:** The safety and efficacy of brolucizumab administered in both eyes concurrently have not been studied. **◆Immunogenicity:** As this is a therapeutic protein, there is a potential for immunogenicity with brolucizumab. Patients should be instructed to inform their physician if they develop symptoms such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light. **◆Concomitant use of other anti VEGF:** There are no data available on the concomitant use of Beovu® with other anti VEGF medicinal products in the same eye. Brolucizumab should not be administered concurrently with other anti VEGF medicinal products (systemic or ocular). **◆Withholding treatment:** In intravitreal anti-VEGF treatments, the dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of: • a decrease in best corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity; • a retinal break; • a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50% of the total lesion area; • performed or planned intraocular surgery within the previous or next 28 days. **◆Retinal pigment epithelial tear:** Risk factors associated with the development of a retinal pigment epithelial tear after anti VEGF therapy for wet AMD include a large and/or high pigment epithelial retinal detachment. When initiating brolucizumab therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears. **◆Rhegmatogenous retinal detachment or macular holes:** Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. **◆Systemic effects following intravitreal use:** Systemic adverse events, including non ocular haemorrhages and arterial thromboembolic events, have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with AMD with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 3 months. Caution should be exercised when treating such patients. **◆Sodium content:** This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free". **◆Driving and using machines:** Beovu® has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances following the intravitreal injection and the associated eye examination. Patients should not drive or use machines until visual function has recovered sufficiently. **Pregnancy, lactation, women of childbearing potential, fertility. Pregnancy:** Although the systemic exposure after ocular administration is very low, brolucizumab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. **Lactation:** Brolucizumab is not recommended during breast feeding and breast feeding should not be started for at least one month after the last dose when stopping treatment with brolucizumab. **Women of childbearing potential:** Women of childbearing potential should use effective contraception during treatment with brolucizumab and for at least one month after the last dose when stopping treatment with brolucizumab. **Fertility:** Based on the mechanism of action of VEGF inhibitors, there is a potential risk for female reproduction, and to embryo/foetal development. **Adverse drug reactions: Common (≥1/100 to <1/10):** Hypersensitivity (including urticaria, rash, pruritus, erythema), visual acuity reduced, retinal haemorrhage, uveitis/iritis, vitreous detachment, retinal tear, cataract, conjunctival haemorrhage, vitreous floaters, eye pain, intraocular pressure increased, conjunctivitis, retinal pigment epithelial tear, vision blurred, corneal abrasion, punctate keratitis. **Uncommon (≥1/1,000 to <1/100):** Blindness, endophthalmitis, retinal artery occlusion, retinal detachment, conjunctival hyperaemia, lacrimation increased, abnormal sensation in eye, detachment of retinal pigment epithelium, vitritis, anterior chamber inflammation, iridocyclitis, anterior chamber flare, corneal oedema, vitreous haemorrhage. **Frequency not known:** Retinal vasculitis, retinal vascular occlusion. **Interactions:** No interaction studies have been performed. **Packs:** Vial: Pack size of 1 vial and 1 blunt filter needle. Pre-filled syringe: Pack size of 1 pre filled syringe. Not all pack sizes may be marketed. **Legal classification:** P15153. Ref: EU Sep 2020

The materials for Beovu® are approved for use only in Hong Kong. Prescribing information may vary depending on local approval in each country/location. Before prescribing any product, always refer to local materials such as the prescribing information and/or the Summary of Product Characteristics (SPC).

For Hong Kong Healthcare Professionals' reference and sole use only.

*The primary efficacy endpoint for the studies was the change from baseline in BCVA at Week 48 as measured by the ETDRS Letter Score, with the primary objective to demonstrate non-inferiority of Beovu vs aflibercept.[1]
†Secondary endpoint in HAWK and HARRIER, confirmatory analysis in HAWK only (1-sided P values for superiority of Beovu).[1,4]

REFERENCES
1. Beovu Prescribing Information HK. Oct 2020. **2.** Dugel PU, Koh A, Ogura Y, et al; on behalf of the HAWK and HARRIER Study Investigators. HAWK and HARRIER. Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2020;127(1):72-84. **3.** Data on file. RTH258-C002 Clinical Study Report. Novartis; 2018. **4.** Data on file. RTH258-C001 Clinical Study Report. Novartis; 2018.

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