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The College of Ophthalmologists of Hong Kong



香港眼科醫學院

EDITORIAL

- Towards a sustainable and better future

ORIGINAL ARTICLE

- Accuracy of the EyeArt artificial intelligence system in detecting referable diabetic retinopathy in patients with diabetes in Hong Kong

PERSPECTIVES

- Consensus on managing center-involving diabetic macular edema in Hong Kong: perspective
- Faricimab to treat neovascular age-related macular degeneration: perspective
- Nutraceuticals for infants with retinopathy of prematurity: perspective
- Different routes of steroidal administration for non-infectious uveitis: perspective

CASE REPORT

- Ulcerated conjunctival mass as an initial presentation of idiopathic orbital inflammatory disease: a case report

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Editor-in-Chief
Jason CS Yam

Correspondence
The College of Ophthalmologists of Hong Kong
Room 802, 8/F, Hong Kong Academy of
Medicine Jockey Club Building
99 Wong Chuk Hang Road
Aberdeen, Hong Kong SAR, China.
Tel (852) 2761 9128
Fax (852) 2715 0089
E-mail: cohk@netvigat.com

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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).

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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.

Towards a sustainable and better future

With over 10000 accesses to our articles in 2023, our online journal platform <https://www.hkjo.hk/> has, on its 8th anniversary, reached a major milestone. We are pleased that our aims of expanding the readership and profile of our journal¹ have been attained. In the smartphone era, readers can easily access our articles anytime, anywhere. To ensure proper preservation of articles, we have recently subscribed to the digital preservation service—Portico.

In contrast, storing and retrieving a print copy of our journal may be less convenient and accessible. With the collective responsibility to reduce environmental impact, the editorial board would like to offer our readers the option to opt out of receiving a print copy, beginning from 2024. Please kindly fill in an online form via the below QR code. We would like to thank our readers for their understanding and support of our sustainability initiatives.

We also wish to remind our trainees (who enter training after 1 January 2020) of the publishing requirement. Trainees are required to publish a first-authored paper before sitting for the part D examination. The *Hong Kong Journal of Ophthalmology* is one of the eligible venues for publishing your work. Furthermore, with generous support from the College and the Timothy Liu Kai Ching Memorial Fund, original articles published in our journal shall be candidates for the prestigious *Hong Kong Journal of Ophthalmology* Best Original Article Award.

On behalf of the editorial board, may we wish all readers a happy, healthy, and successful year in 2024.

Dr Au Ka Hong, MHM (UNSW), FHKAM (Ophthalmology); Dr Yam Cheuk Sing Jason, MD (CUHK), FHKAM (Ophthalmology)

Reference

1. Wong IY. A new home for the Hong Kong Journal of Ophthalmology. *Hong Kong J Ophthalmol* 2016;20:5-6.

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Accuracy of the EyeArt artificial intelligence system in detecting referable diabetic retinopathy in patients with diabetes in Hong Kong

Sunny Chi Lik Au^{1,2}, MBChB, MRCSEd, FCOphthHK, FHKAM (Ophthalmology); George Tsz Ho Shum³, MBBS, MRCP(UK), FHKCP; Steffi Shing Yee Chong^{1,2}, MBBS, MRCSEd; Callie Ka Li Ko^{1,2}, MBBS, FCOphthHK, FHKAM (Ophthalmology)

¹Department of Ophthalmology, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China

²Department of Ophthalmology, Tung Wah Eastern Hospital, Hong Kong SAR, China

³Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China

Correspondence and reprint requests:

Sunny Chi Lik Au, 9/F, MO Office, Lo Ka Chow Memorial Ophthalmic Centre, Tung Wah Eastern Hospital, 19 Eastern Hospital Road, Causeway Bay, Hong Kong SAR, China. Email: kilihcua@gmail.com

Abstract

Objective: This study evaluated the real-world performance in an Asian population with diabetes mellitus (DM) of the EyeArt system, which is the only United States Food and Drug Administration–approved system available in Hong Kong.

Methods: Fundus photographs taken from December 2020 to June 2021 during a diabetic retinopathy (DR) screening program in patients with DM who attended Pamela Youde Nethersole Eastern Hospital in Hong Kong were retrieved. Two vitreoretinal-trained ophthalmologists independently graded the fundus photographs for DR and concomitant pathologies. Discrepancies were resolved through discussion with a senior vitreoretinal ophthalmologist for a final decision. Fundus photographs (in jpg format) were then uploaded to the EyeArt AI system. The EyeArt system's sensitivity and specificity on detecting (1) referable DR (moderate or severe non-proliferative DR, proliferative DR, or diabetic macular edema [DME]) and (2) any DR or DME were calculated based on the ophthalmologists' diagnoses (the gold standard).

Results: 23 men and 79 women (93 Chinese, 3 Pakistanis,

2 Thais, and 4 Indonesians) aged 25 to 77 years with type 1 (n=8) or type 2 (n=94) DM were included for analysis. The mean duration of DM was 4.9 years; 56 (54.9%) patients were newly diagnosed with DM. 33 (32.4%) patients were taking ≥ 1 (up to 4) oral hypoglycemic agents; none were taking ≥ 5 . 16 (15.7%) patients required both oral hypoglycemic agents and insulin for DM control; 31 (30.4%) patients injected insulin every day. As diagnosed by the ophthalmologists, 41 (20.1%) of 204 eyes had DR and/or DME, whereas 26 (25.5%) of 102 patients had referable DR. There was no discrepancy between the two ophthalmologists' gradings. On detecting referable DR, the EyeArt system had 96.2% sensitivity, 94.7% specificity, 86.2% positive predictive value, 98.6% negative predictive value, and 95.1% accuracy. On detecting any DR or DME, the EyeArt system had 92.7% sensitivity, 93.7% specificity, 79.2% positive predictive value, 98.0% negative predictive value, and 93.5% accuracy.

Conclusion: The EyeArt system is a reliable AI tool for DR screening in patients with DM in Hong Kong. Its usage in primary care and public healthcare programs should be considered.

Key words: Artificial intelligence; Diabetic retinopathy; Macular edema

Introduction

Artificial intelligence (AI) models intelligent behavior with minimal human intervention.¹ AI is increasingly used in clinical practice to improve healthcare services by expediting processes with greater accuracy.² Its applications include informatics approaches via machine learning and deep learning in clinical information management.³ Image analysis is one such technology.⁴

In Hong Kong, diabetes mellitus (DM) is increasingly prevalent; DM and its related morbidities are important primary healthcare issues.⁵ Diabetic retinopathy (DR) is the most common complication of DM.⁶ Among patients with DM in Hong Kong, the prevalence of DR is 39%.⁷ Screening for DR and timely treatment are essential to avoid vision loss, particularly for working-age patients with DM.⁷

Automated DR-detection algorithms have been developed to stratify patients' risks in terms of vision-threatening DR and diabetic macular edema (DME).^{8,9} AI can facilitate the integration of community, primary, and specialist eye care services, optimize the flow of patients within healthcare networks, and improve the efficiency of DR management.¹⁰ Nonetheless, applying AI in real-world clinical settings is challenging.

As of 2022, the only United States Food and Drug Administration (FDA)-approved DR screening system available in Hong Kong was the EyeArt AI system (Eyenuk, Los Angeles [CA], USA). There are few extant studies examining the use of EyeArt in Asian populations.^{11,12} Retinas in Asians are believed to differ from those in Caucasians, given the much higher prevalence of myopia among Asians.¹³ This study aims to evaluate the accuracy of the EyeArt in detecting referable DR in patients with DM in Hong Kong.

Materials and methods

In April 2022, fundus photographs from patients with DM who attended Pamela Youde Nethersole Eastern Hospital in Hong Kong were retrieved after removing all patient identifiers. All the fundus photographs were taken by the non-mydratic Auto Fundus Camera 330 (Nidek, Gamagori, Japan) between December 2020 and June 2021. Two photographs were taken for each eye: one centered on the macula and the other centered at the optic disc. Poor-quality photographs with the presence of cataracts or media opacities were not excluded to reflect real-world conditions. Eyes with retinal vascular diseases (such as retinal vein occlusion, age-related macular degeneration, and retinal artery microaneurysm) and eyes with missing fundus photographs were excluded.

Data on patient demographics (age, sex, ethnicity, and smoking history), diabetic status and control, other metabolic diseases, medication and medical history, and

ophthalmic history were collected. Data were blinded from both the grading ophthalmologists and the AI operator. Two ophthalmologists, specialized in vitreoretinal diseases, independently graded the fundus photographs for DR and concomitant pathologies, such as cataracts and macular diseases. Discrepancies were resolved through discussion with a senior vitreoretinal ophthalmologist for a final decision.

Fundus photographs (in jpg format) of included patients were then uploaded to the EyeArt AI system (version 2.1.0) by a resident trainee. Items investigated included the photographs' gradeability, DR severity, presence of DME, and any ophthalmologist-referable recommendations (**Figure**). Gradings of the fundus photographs by both the ophthalmologists and EyeArt were based on the 2017 International Council of Ophthalmology Guidelines for Diabetic Eye Care recommendations.¹⁴ The EyeArt system's sensitivity and specificity on detecting (1) referable DR (moderate or severe non-proliferative DR, proliferative DR, or DME) and (2) any DR or DME were calculated based on the ophthalmologists' diagnoses (the gold standard).

EyeArt's diagnostic sensitivity and specificity have been reported to be 96% and 88%, respectively.¹¹ In this study, sensitivity and specificity were calculated through the respective equations: $TP + FN = Z^2 \times [\text{sensitivity} \times (1 - \text{sensitivity}) / W^2]$ and $TN + FP = Z^2 \times [\text{specificity} \times (1 - \text{specificity}) / W^2]$, where Z is set to 1.96 for the normal distribution value, corresponding to the 95% confidence interval (CI). W, the maximum acceptable width of the 95% CI, is set to 10%,¹⁵ and the expected sensitivity and specificity are based on estimates from the available information (ie, 95%). $TP + FN$ is equal to 14.751744 and $TN + FP$ is equal to 40.567296. The sample size required for sensitivity and specificity is $[TP + FN / P]$ and $[TN + FP / (1 - P)]$, respectively,¹⁵ in which P is the prevalence of DR in Chinese populations in Hong Kong. In a large-scale study of 174532 patients, the estimated prevalence of DR was 39%.⁷ Thus, 37 and 65 patients were required to determine sensitivity and specificity, respectively, with a total required sample size of 102. Statistical analyses were performed using SPSS (version 27, IBM, Armonk, [NY], USA).

Results

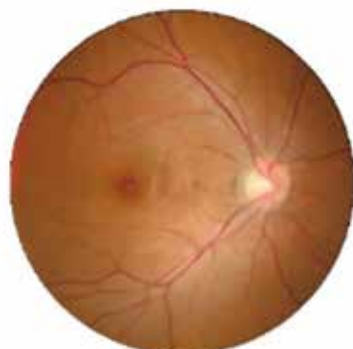
Of 112 patients' records retrieved, 10 were excluded owing to non-Asian patients (n=2), an incomplete set of fundus photographs (n=1), retinal vein occlusion (n=1), active age-related macular degeneration (n=5), or retinal artery microaneurysm (n=1). The remaining 23 men and 79 women (93 Chinese, 3 Pakistanis, 2 Thais, and 4 Indonesians) aged 25 to 77 years with type 1 (n=8) or type 2 (n=94) DM were included for analysis (**Table 1**). The mean duration of DM was 4.9 years; 56 (54.9%) patients were newly diagnosed with DM. 33 (32.4%) patients were taking ≥ 1 (up to 4) oral hypoglycemic agents; none were taking ≥ 5 . The most commonly used oral hypoglycemic agent was metformin (biguanide) [n=30], followed by sodium-glucose transport

EyeArt Diabetic Retinopathy (DR) Exam Result Summary*

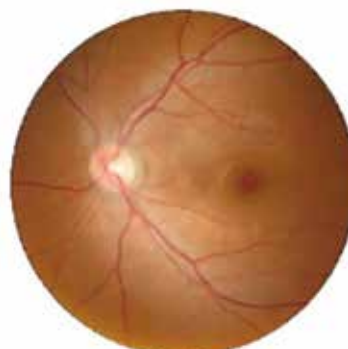
Negative for referable diabetic retinopathy.

Right Eye: No apparent signs of DR [0.0] detected

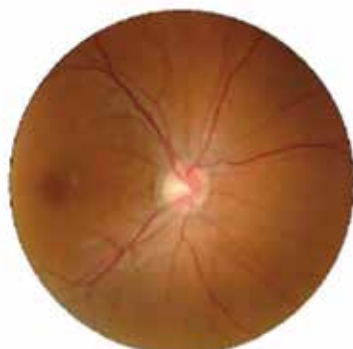
Left Eye: No apparent signs of DR [0.0] detected



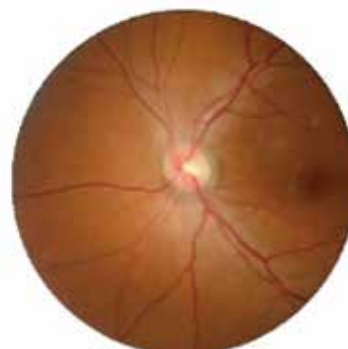
Macula Centered, Right Eye



Macula Centered, Left Eye



Optic Nerve Head Centered, Right Eye



Optic Nerve Head Centered, Left Eye

*Do not use the above thumbnail images for diagnostic purposes.

Notes

A negative result for referable diabetic retinopathy indicates a low risk for moderate non-proliferative DR, severe non-proliferative DR, proliferative DR, and markers for diabetic macular edema.

Recommended scheduling of next diabetic eye screening, per national guidelines and/or ICO Guidelines for Diabetic Eye Care (2017).

Figure. Example report of the EyeArt system

protein 2 inhibitors (n=8), dipeptidyl peptidase IV inhibitors (n=7), sulfonylureas (n=7), thiazolidinediones (n=4), and glucagon-like peptide 1 receptor agonists (n=3). 16 (15.7%) patients required both oral hypoglycemic agents and insulin for DM control; 31 (30.4%) patients injected insulin every day. The mean hemoglobin A1c was 7.0%. Seven (6.9%) patients were active smokers, and 17 (16.7%) patients were ex-smokers.

As diagnosed by the ophthalmologists, 41 (20.1%) of 204 eyes had DR and/or DME, and five (2.5%) eyes were ungradable owing to media opacity (**Table 2**), whereas 26 (25.5%) of 102 patients had referable DR. There was no discrepancy between the two ophthalmologists' gradings. Five (2.5%) eyes had laser marks on the retina, which

reflects a history of panretinal photocoagulation treatment for proliferative DR. There were no cases of vitreous, pre-retinal, or subhyaloid hemorrhages.

On detecting referable DR, the EyeArt system had 96.2% (95% CI=80.4%-99.9%) sensitivity, 94.7% (95% CI=87.1%-98.6%) specificity, 86.2% (95% CI=70.6%-94.2%) positive predictive value, 98.6% (95% CI=91.3%-99.8%) negative predictive value, and 95.1% (95% CI=88.9%-98.4%) accuracy (**Table 3**). On detecting any DR or DME, the EyeArt system had 92.7% (95% CI=80.1%-98.5%) sensitivity, 93.7% (95% CI=88.7%-96.9%) specificity, 79.2% (95% CI=67.5%-87.5%) positive predictive value, 98.0% (95% CI=94.3%-99.3%) negative predictive value, and 93.5% (95% CI=89.1%-96.5%) accuracy (**Table 4**).

Table 1. Patient characteristics (n=102)

Characteristic	Value*
Age, y	44.2±13.8 (25-77)
Body mass index, kg/m ²	25.7±4.8 (15.0-42.4)
Duration of diabetes mellitus, y	4.9±8.1 (0-35)
Hemoglobin A1c, %	7.0±2.9 (4.5-19.0)
No. of oral hypoglycemic agents taken	0.6±1.1 (0-4)
Triglycerides, mmol/L	1.38±0.77 (0.51-4.38)
High-density lipoprotein, mmol/L	1.19±0.33 (0.40-1.83)
Calculated low-density lipoprotein, mmol/L	2.30±0.67 (1.13-3.71)

* Data are presented as mean ± standard deviation (range)

Table 2. Diabetic retinopathy gradings of 204 eyes as determined by ophthalmologists

Diabetic retinopathy	No. of eyes	Referable
Not apparent	158	No
Mild non-proliferative	7	No
Moderate non-proliferative	20	Yes
Severe non-proliferative	5	Yes
Proliferative	9	Yes
Diabetic macular edema*	4	Yes
Ungradable	5	Yes

* Eyes with diabetic macular edema also have diabetic retinopathy

Table 3. Accuracy of the EyeArt system in detecting referable diabetic retinopathy, compared with the gold standard by ophthalmologists

No. of patients (n=102) with referable diabetic retinopathy*		
EyeArt	Ophthalmologists	
	Yes	No
Yes	25	4
No	1	72

* Five eyes that were ungradable were included to simulate real-world conditions

Table 4. Accuracy of the EyeArt system in detecting any diabetic retinopathy or diabetic macular edema, compared with the gold standard by ophthalmologists

No. of eyes (n=199) with any diabetic retinopathy or diabetic macular edema*		
EyeArt	Ophthalmologists	
	Yes	No
Yes	38	10
No	3	148

* Five eyes were ungradable

Discussion

The EyeArt system exhibits high sensitivity and specificity on detecting DME and DR, including referable DR, in patients with DM in Hong Kong. It exceeds the benchmark required for graders in primary healthcare settings (sensitivity of ≥95% and specificity of ≥85%).⁷ In our sample, sensitivity is greater as determined by the EyeArt than that based on our retrospective review of patients' records (96.2% vs 69.2%).

Of the handful of commercially available AI systems that have been FDA-approved for DR screening, only IDx-DR (Digital Diagnostics, Coralville [IA], USA) and EyeArt are supported by searchable scientific publications.⁹ IDx-DR is not yet available in Hong Kong. EyeArt was similarly unavailable before our study in 2022, but it has become the only FDA-approved AI system for DR screening currently in use in Hong Kong. There is no previous study of EyeArt in a purely Asian population. To the best of our knowledge, the present study is the first to evaluate the real-world performance of an FDA-approved AI system for DR screening in an Asian population.

We used real-world data from a 7-month public screening service to reflect the reality of implementing this diagnostic AI tool in daily clinical practice. The high proportion (more than half) of newly diagnosed DM patients might be related to our hospital setting,¹⁶ as these DM patients might be at the stage of oral hypoglycemic agents and insulin titration and have not yet stepped down to family medicine or general outpatient clinics for regular medication refills. However, this phenomenon could also result from better patient compliance with DR screening soon after diagnosis.

Additionally, the mean patient age of 44.2 years in our study is also younger than that of 60 years in previous studies.^{16,17} This might explain why our patients have a lower prevalence of DR than previously published data.⁷ Our relatively younger DM population also accounts for the lower percentage (2.5%) of ungradable photographs owing to the presence of cataracts.

Our study reported a higher proportion of referable DR than a study in large-scale primary care settings did (25.5% vs 9.8%).⁷ This could be because our study was conducted in a tertiary hospital that comprises pediatricians, renal dialysis services, orthopedic surgeons, ophthalmologists, intensive care units, and even the sole hyperbaric oxygen service for diabetic foot ulcers to manage all kinds of diabetic complications.¹⁸ Difficult and complicated DM cases tend to stay in hospital settings rather than family medicine or general outpatient clinics, where fewer oral hypoglycemic agents and insulins are available.

AI DR screening systems have advantages over human graders. First, AI systems can grade photographs non-stop 24 hours a day, 7 days a week.¹⁹ This is important to tackle the growing demand for public DR screening services that comes with the rise in DM population; increased service

provision means shorter waiting times.²⁰ Second, training graders takes time,²¹ and the high turnover of personnel is a big issue.²² Third, human graders perform inconsistently owing to mood changes or time constraints; they can be absent from work during the COVID-19 outbreak, for example.

Despite the advantages of AI DR screening systems, the risks associated with cybersecurity and dependence on overseas private commercial products should not be overlooked.²³⁻²⁵ The present study is limited by the lack of stereoscopic fundus photographs or optical coherence tomography for DME diagnosis. Human grading based purely on two-dimensional fundus photographs may give a high false positive rate of DME.^{26,27} Therefore, EyeArt's genuine diagnostic accuracy of DME requires further validation in future studies.

Conclusion

The EyeArt system is a reliable AI tool for DR screening in patients with DM in Hong Kong. Its usage in primary care and public healthcare programs should be considered.

Contributors

SCLA designed the study, acquired and analyzed the data, and drafted the manuscript. GTHS acquired and analyzed the data. SSYC acquired the data. CKLK acquired the data 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.

Conflicts of interest

As editors of the journal, SCLA and CKLK were not involved in the peer review process. Other 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 Hong Kong East Cluster Research Ethics Committee (reference: HKEC-REC-2022-019). All research protocols were conducted in accordance with the Declaration of Helsinki.

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THE
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Consensus on managing center-involving diabetic macular edema in Hong Kong: perspective

Nicholas Fung¹, BA, FHKAM (Ophthalmology), FCOphthHK, MRCS, MBChB; Mary Ho², FCOphthHK, FHKAM (Ophthalmology); Gemmy CM Cheung³, FRCOphth; Alvin KH Kwok⁴, MD, PhD, FHKAM (Ophthalmology), FRCOphth, FCOphth, FCSHK, FRCSEd, PDip Epidemiology and Biostatistics, MBBS; Gary KY Lee⁵, MBBS, MRCSEd, FHKAM (Ophthalmology); Danny SC Ng⁶, FRCSEd, FCOphth, FHKAM (Ophthalmology), MPH, MBBS; Pui Pui Yip⁷, FHKAM (Ophthalmology), FCOphth, MBChB, MMedSc, MRCS; Raymond Wong⁸, FHKAM (Ophthalmology), FCOphthHK; Timothy YY Lai^{6,9}, MD, FRCOphth, FRCSEd

¹Department of Ophthalmology, The University of Hong Kong, Hong Kong SAR, China

²Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong SAR, China

³Medical Retina Department, Singapore Eye Research Institute, Singapore National Eye Centre, Singapore

⁴Hong Kong Sanatorium & Hospital, Hong Kong SAR, China

⁵The Hong Kong Ophthalmic Associates, Hong Kong SAR, China

⁶Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China

⁷Champion Eye and Refractive Surgery Centre, Hong Kong SAR, China

⁸C-MER Dennis Lam and Partners Eye Center, Hong Kong SAR, China

⁹2010 Retina and Macula Centre, Hong Kong SAR, China

Correspondence and reprint requests:

Nicholas Fung, Room 301, Level 3, Block B, Cyberport 4, 100 Cyberport Road, Hong Kong SAR, China. Email: nfung@hku.hk

Abstract

Diabetic macular edema is a common cause of vision loss in the working-age population, and its prevalence is increasing in Asian countries. Managing diabetic macular edema encompasses effective control of systemic factors and intraocular treatment including anti-vascular endothelial growth factor therapy, corticosteroid implants, and laser photocoagulation. Based on several guidelines and the available evidence, we present consensus on managing diabetic macular edema in Hong Kong to ensure optimal anatomical and visual outcomes. Although anti-vascular endothelial growth factor agents are recommended first-line treatment for patients with diabetic macular edema experiencing vision loss, the frequent dosing regimen imposes great clinical and patient burden. Longer-acting anti-vascular endothelial growth factor agents are needed to allow for longer intervals between treatments. As demonstrated in the KITE and KESTREL studies, brolicizumab, an anti-vascular endothelial growth factor A agent, is associated

with fewer cases of intraretinal or subretinal fluid than aflibercept, despite fewer injections. Similarly, faricimab, a bispecific antibody targeting both vascular endothelial growth factor A and angiopoietin-2, demonstrated comparable vision gains with longer treatment intervals and larger improvements in anatomical outcome in the YOSEMITE and RHINE trials. Early intensive anti-vascular endothelial growth factor therapy leads to greater improvements in visual acuity and anatomical outcomes. Patients who respond inadequately to anti-vascular endothelial growth factor therapy, as monitored by optical coherence tomography, should switch treatment modality.

Key words: Angiopoietin-2; Intravitreal injections; Laser therapy; Vascular endothelial growth factors; Visual acuity

Introduction

Diabetic macular edema (DME) may cause vision loss.¹ The prevalence of DME in Asian populations (despite being lower than in other populations) is expected to increase as the incidence of diabetes increases.² Effective systemic

control, managing comorbidities of diabetes, and ocular treatment are important in DME management.

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents are recommended first-line therapy for patients with center-involving DME,³⁻⁶ but approaches to treatment posology and therapy selection differ.¹ Moreover, these treatments are costly and thus access may be limited for some patients who may in turn develop more advanced forms of the disease.²

Anti-VEGF agents (aflibercept, bevacizumab, and ranibizumab) can improve visual acuity (VA) in patients with DME.⁷ However, these agents have limited potency and durability, necessitating frequent dosing regimens.⁸ Patients receiving repeated intravitreal therapy (IVT) injections suffer a heavy medical burden, involving lengthy wait times for outpatient clinics and multiple appointments.⁸ Further research into longer-acting anti-VEGF agents is warranted.

Brolucizumab and faricimab are comparably effective to aflibercept, potentially necessitating fewer injections and enabling longer intervals between treatments.^{9,10} A group of experts reviewed the recent clinical and real-world data to reach a consensus on the role of current therapeutic agents in managing DME.

Methodology

Eight ophthalmologists from Hong Kong and one from Singapore convened in September 2022 to seek consensus on recommendations for managing DME in Hong Kong based on the published evidence and their clinical experience. Before the meeting, the experts reviewed the literature on diagnosing and managing DME. Three of the experts then developed recommendation statements, which were voted on and discussed at the meeting. Each proposed recommendation was voted on using a five-point Likert scale (accept completely, accept with some reservation, accept with major reservation, reject with reservation, reject completely).¹¹ No further changes were necessary if $\geq 80\%$ voted 'accept completely' or 'accept with some reservation'. Recommendations with $< 80\%$ acceptance threshold were revised and then voted again after the meeting. The wording and/or content of the rejected statements were adjusted (Table 1). The approved statements were the expert panel's consensus recommendations for managing DME in Hong Kong. A treatment algorithm relevant to Hong Kong's population was then proposed (Figure 1).

DME definition and treatment goals

Statement 1: DME is a multifactorial disease that may require inhibition of multiple pathways for optimal management

Chronic hyperglycemia activates several pathways that contribute to vascular and tissue damage in organs including the eye.¹² DME is a complex and multifactorial condition, characterized by the breakdown of the blood-retinal barrier,

which allows fluid and serum macromolecules to accumulate in the intercellular space.¹³

The synergistic effects of several growth factors promote angiogenesis, hyperpermeability, and inflammation in diabetic retinopathy, suggesting that inhibiting a single pathway may not sufficiently control DME. Agents that inhibit pathways other than VEGF alone are needed.¹⁴⁻¹⁸

Statement 2: Systemic control is an essential treatment goal when managing DME

Poor control of diabetes comorbidities, including hypertension, renal impairment, and hyperlipidemia, may result in a poor prognosis of diabetic retinopathy. Controlling blood glucose levels, blood pressure, and cholesterol levels can slow or stop diabetic maculopathy from progressing.¹⁹

Statement 3: DME treatment should aim for the best visual outcome with edema improvement while minimizing the treatment burden

Statement 4: Regular optical coherence tomography monitoring is recommended to assess treatment response

Optical coherence tomography (OCT) is widely used to monitor DME and can be used to personalize DME treatment regimens.²⁰ OCT can assess anatomical parameters such as macular thickness and the presence of hyperreflective foci or intraretinal and subretinal fluid, enabling identification of patients who can benefit from the treat-and-extend strategy to reduce their treatment burden.²¹

Statement 5: Anti-VEGF treatment is considered ineffective if reduction in central subfield thickness is $< 10\%$ after at least three to six injections

Several studies evaluating anti-VEGFs for DME define a limited early response as a $\leq 10\%$ reduction in central subfield thickness (CST) after three to six injections. A post-hoc analysis of the VISTA and VIVID trials investigated patients with DME who had suboptimal responses at week 12 following 3-monthly aflibercept injections or one laser treatment.²² Aflibercept significantly improved best-corrected visual acuity (BCVA) by week 100 relative to laser treatment in several eyes with DME.²² In another study that applied the same indication for limited early response to anti-VEGF agents, aflibercept was superior to bevacizumab and ranibizumab in improving vision outcomes; all three anti-VEGF agents had comparable safety profiles.²³

Statement 6: Switching therapy is an option for managing patients with refractory DME

Anti-VEGF agents prevent the activation of VEGF receptors on endothelial cells and thus stop vascular endothelial hyperplasia from developing, thereby counteracting DME pathogenesis.²⁴

Current guidelines recommend monthly monitoring during the first 6 months of anti-VEGF treatment.¹⁴ Monitoring should continue thereafter because worsening VA and CST

Table 1. Voting results on consensus statements on managing center-involving diabetic macular edema (DME) in Hong Kong

Statement	% of ophthalmologists (n=9)*				
	Accept completely	Accept with some reservation	Accept with major reservation	Reject with reservation	Reject completely
1: DME is a multifactorial disease that may require inhibition of multiple pathways for optimal management	100	-	-	-	-
2: Systemic control is an essential treatment goal when managing DME	100	-	-	-	-
3: DME treatment should aim for the best visual outcome with edema improvement while minimizing the treatment burden	100	-	-	-	-
4: Regular optical coherence tomography monitoring is recommended to assess treatment response	75	25	-	-	-
5: Anti-VEGF treatment is considered ineffective if reduction in central subfield thickness is <10% after at least three to six injections	75	25	-	-	-
6: Switching therapy is an option for managing patients with refractory DME	100	-	-	-	-
7: Anti-VEGF agents, with or without ANG-2 inhibition, are recommended first-line treatment for center-involving DME	87.5	12.5	-	-	-
8: A good safety profile should be considered when selecting a first-line intravitreal therapy	100	-	-	-	-
9: Intensive intravitreal therapy during the first year is important to maximize patients' visual improvement and minimize the number of injections in subsequent years	100	-	-	-	-
10: Fixed dose, treat-and-extend, or as-needed regimens may be considered for anti-VEGF agents after the loading dose, based on anatomical and functional assessments	100	-	-	-	-
11: Switching between intravitreal therapy agents could be beneficial for patients with refractory DME	100	-	-	-	-
12: Focal laser treatment is an option for patients with non-center-involving DME and/or extrafoveal leaking microaneurysms	100	-	-	-	-
13: Steroid implants can be used as a first-line treatment for pseudophakic patients without a history of glaucoma	75	25	-	-	-
14: Focal laser and grid laser can be a treatment option with or without anti-VEGF therapy or other combination	87.5	12.5	-	-	-
15: Pars plana vitrectomy may be performed in patients with vitreomacular traction or epiretinal membrane	88	13	-	-	-

Abbreviations: ANG-2=angiopoietin-2; DME=diabetic macular edema; VEGF=vascular endothelial growth factor

* Consensus was defined as 80% of ophthalmologists selecting 'accept completely' or 'accept with some reservation'. Statements that did not achieve consensus are not included.

rebound are common.^{1,4} Beyond the first year, intervals between treatments may gradually extend for patients with stable VA and CST.^{1,4}

Although 33% to 45% of patients with DME achieve ≥ 3 lines of visual improvement after intensive anti-VEGF injections,^{3,6} some patients do not respond sufficiently. Suboptimal responses can be attributed to other factors involved in DME's pathogenesis that have not been fully addressed, including the upregulated intraocular inflammation cascade.²⁵ Differences in VEGF gene expression may also be a contributing factor; thus, combining therapies or switching to an anti-VEGF agent with a different mechanism of action is recommended.²⁶

Treatment selection: IVT injections (anti-VEGF and anti-VEGF/ANG-2)

Statement 7: Anti-VEGF agents, with or without ANG-2 inhibition, are recommended first-line treatment for center-involving DME

Aflibercept, ranibizumab, and bevacizumab have shown to improve VA after 2 years of treatment.²⁷ Aflibercept and ranibizumab are the preferred first-line therapies in patients with a baseline BCVA letter score of <69; the addition of off-label bevacizumab is recommended for those with a baseline BCVA of ≥ 69 .²⁷ Asia-Pacific regional experts agreed on using anti-VEGF agents as the first-line treatment for center-involving DME with vision loss and using

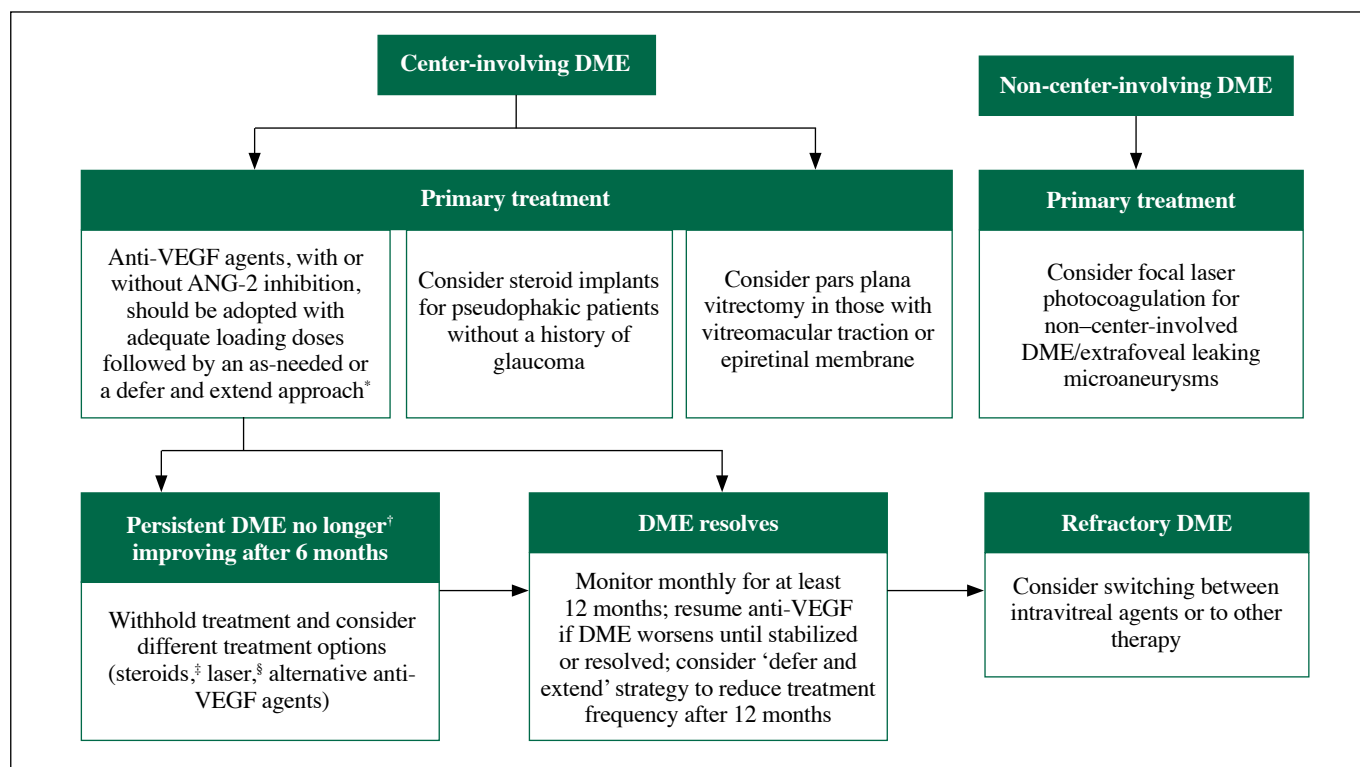


Figure. Suggested treatment algorithm for managing center-involving diabetic macular edema in Hong Kong

Abbreviations: ANG-2=angiopoietin-2; DME=diabetic macular edema; VEGF=vascular endothelial growth factor

* An acceptable safety profile should be considered when selecting a first-line intravitreal. Fixed dose, treat-and-extend, or as-needed regimens may be considered for anti-VEGF agents after the loading dose, based on anatomical and functional assessments.

† An inadequate response to anti-VEGF treatment is defined as a central subfield thickness reduction $\leq 10\%$ after 3 to 6 injections.

‡ Steroids may be accompanied by cataract formation and increase in intraocular pressure.

§ Focal and grid laser photocoagulation have been associated with a significant long-term risk of vision loss.

corticosteroids as a secondary treatment.²⁸ Nonetheless, guidelines on managing DME have not been established, although multiple trials have demonstrated the superiority of anti-VEGF therapy over laser therapy in improving BCVA.

In two randomized phase III trials (VIVID and VISTA), patients with DME received either aflibercept injections every 4 or 8 weeks (after 5 monthly injections) or macular laser photocoagulation therapy. Both regimens of aflibercept were superior to laser therapy in improving mean BCVA at week 148.²⁹ The efficacy of anti-VEGF agents was also demonstrated in the RISE and RIDE trials, which were randomized phase III sham injection-controlled trials investigating ranibizumab injection in patients with DME.³⁰ Significantly more patients receiving ranibizumab gained ≥ 15 letters in BCVA by 24 months.³⁰ Bevacizumab has shown to effectively treat patients with refractory and treatment-naïve DME, either as a monotherapy or in combination with triamcinolone acetonide or laser photocoagulation.³¹⁻³⁴

KITE and KESTREL were randomized phase III clinical studies comparing brolucizumab and aflibercept for the treatment of DME.³⁵ A loading dose of five brolucizumab

injections every 6 weeks for the first 24 weeks was followed by a maintenance dose every 8 or 12 weeks depending on disease activity until week 72 (KESTREL) or week 100 (KITE).³⁵ Despite involving fewer injections, brolucizumab met the primary endpoint (a mean change in BCVA non-inferior to aflibercept).³⁵ Occurrence of intraretinal fluid or subretinal fibrosis was fewer with brolucizumab than aflibercept.³⁵ Brolucizumab's safety profile at week 100 was consistent with published data from year 1.^{35,36}

The ANG-2 pathway should be targeted for managing DME, as levels of ANG-2 are upregulated in many retinal diseases.^{37,38} Faricimab is the first bispecific-antibody intraocular DME agent targeting both ANG-2 and VEGF-A. Simultaneous inhibition may stabilize blood vessels and reduce neovascularization, resulting in improved potency and durability against retinal diseases. Its large molecular size increases its half-life in the vitreous fluid. The modified inactive fragment crystallizable domain reduces systemic exposure and pro-inflammatory responses.³⁷ Hong Kong clinical experts believe that faricimab may be an effective first-line treatment for DME owing to its long-acting efficacy.

YOSEMITE and RHINE were double-blinded phase III trials in which patients with DME were randomized to receive injections of either faricimab (every 8 weeks or according to personalized treatment intervals) or aflibercept (every 8 weeks).¹⁰ During the loading phase, patients in the faricimab group received injection every 4 weeks until they attained a CST of <325 µm or after week 12.¹⁰ From week 12 onwards, dosing intervals could be maintained, extended, or reduced, depending on responses in CST and BCVA.¹⁰ Over the 56-week treatment period, 62% of patients completed a full dosing cycle of every 12 weeks and maintained or extended to every 16 weeks.¹⁰ The proportion of patients receiving faricimab every 16 weeks increased by 7.2% (YOSEMITE) and 13.5% (RHINE) between weeks 52 and 96.¹⁰ Faricimab elicited greater reductions in CST than aflibercept during 2 years of treatment.¹⁰ RHONE-X, a 4-year follow-up study of YOSEMITE and RHINE, is ongoing.³⁹ YOSEMITE and RHINE remain the only phase III studies comparing faricimab with aflibercept for the treatment of DME.¹⁰ Additional comparative effectiveness trials in clinical and real-world settings are needed.

The 2022 National Institute for Health and Care Excellence guideline recommends aflibercept, ranibizumab, brolucizumab, or faricimab for adult patients with DME to treat visual impairment and a central retinal thickness of ≥400 µm at the start of treatment.⁴⁰⁻⁴³ However, intraocular inflammation is a potential adverse event of brolucizumab.⁴⁰ The Australian Pharmaceutical Benefits Advisory Committee proposed inclusion of brolucizumab and faricimab in the authority-required listing for the treatment of visual impairment in DME.^{44,45}

Statement 8: A good safety profile should be considered when selecting a first-line IVT

Large randomized controlled trials have not reported any major safety concerns regarding anti-VEGF agents for DME.² However, a meta-analysis of anti-VEGF agents, including aflibercept and ranibizumab, revealed that patients at high risk of atherothrombotic disease who have received these agents for 2 years have a potentially increased risk of mortality and cerebrovascular incidents.⁴⁶ The long-term KITE and KESTREL studies also reported new cases of retinal vasculitis after first-line treatment with brolucizumab.³⁵ Faricimab and aflibercept both demonstrated acceptable, comparable safety profiles in the

YOSEMITE and RHINE studies: the exposure-adjusted rates of ocular and non-ocular adverse events were similar between treatment regimens.¹⁰

Statement 9: Intensive IVT during the first year is important to maximize patients' visual improvement and minimize the number of injections in subsequent years

Statement 10: Fixed dose, treat-and-extend, or as-needed regimens may be considered for anti-VEGF agents after the loading dose, based on anatomical and functional assessments

Early intensive treatment is associated with improved visual outcomes (Table 2).⁴⁷⁻⁴⁹ This approach is supported by the results of the Protocol T trial, which recommends early intensive dosing intervals (every 4 weeks) for the first 6 months.² If the patient's condition is stable, the dosing interval can be extended on an as-needed basis at week 24, followed by a monitor-and-extend approach in the second year.² After intensive treatment in the first year, fewer anti-VEGF injections were needed in the second year (a median of 5 to 6 injections), compared with the first year (a median of 9 to 10 injections).^{7,27}

A Hong Kong panel recommended initiating anti-VEGF injections monthly for the first 6 months, except for (<5% of) patients who have a VA of 20/20 or better and a normal OCT-detected CST after two consecutive injections.¹

Given the practical challenges of early intensive treatment, less frequent dosing may be beneficial following the loading phase.² Longer dosing intervals may translate to fewer physician visits, thereby reducing the treatment burden without compromising effectiveness.^{7,27} For example, efficacy is comparable between every 4 weeks and every 8 weeks aflibercept administration. In the RISE and RIDE trials, ranibizumab was associated with vision improvements after 1 or 3 years of treatment, and the improvements were sustained at the 4.5-year follow-up, with a significantly reduced treatment frequency.⁵⁰

Statement 11: Switching between IVT agents could be beneficial for patients with refractory DME

Refractory DME is often defined as a central retinal thickness of >300 µm or a <10% reduction in CST after

Table 2. Improvements in visual acuity and treatment frequency in the first year

Study	Year	Anti-vascular endothelial growth factor agent	Mean No. of injections in the first year	Mean improvement in best-corrected visual acuity after 1 year, No. of letters
Protocol I ⁴⁷	2010	Ranibizumab + prompt laser	8	9.0
Protocol I ⁴⁷	2010	Ranibizumab + deferred laser	9	9.0
RISE and RIDE ⁴⁸	2012	Ranibizumab	10.9	11.1
VIVID and VISTA ⁴⁹	2014	Aflibercept	12	11.6

at least three to six anti-VEGF injections.²⁶ Approximately 40% of patients are deemed to have refractory DME after 2 years of monthly intravitreal ranibizumab treatment.⁵¹ Patients with refractory disease could benefit from intravitreal corticosteroids, focal/grid laser therapy, or an alternative anti-VEGF agent.⁵¹ In a large prospective study, BCVA significantly improved 3 to 6 months after switching from intravitreal bevacizumab to intravitreal ranibizumab, and the improvements were sustained throughout the first year of treatment.²⁶ Switching from intravitreal aflibercept to intravitreal bevacizumab or intravitreal ranibizumab (because of a poor response) improved CST.²⁶ In patients who responded poorly to intravitreal aflibercept, more patients who switched to intravitreal faricimab achieved a central macular thickness of <300 µm without any OCT-detected retinal edema at 4 months, compared with those who stayed on intravitreal aflibercept (37.5% vs 3.7%, $p=0.001$).⁵² Moreover, an almost four-fold increase in VA gain (≥ 2 lines) occurred among patients who switched to intravitreal faricimab, compared with those who continued on intravitreal aflibercept.⁵²

Statement 12: Focal laser treatment is an option for patients with non-center-involving DME and/or extrafoveal leaking microaneurysms

Focal macular laser photocoagulation significantly improved Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores at 12 months in patients with non-center-involving DME and leakage from microaneurysms, compared with patients who did not undergo any treatment.⁵³

Statement 13: Steroid implants can be used as a first-line treatment for pseudophakic patients without a history of glaucoma

Despite frequent anti-VEGF treatment, numerous patients with DME cannot achieve a dry macula. Intravitreal dexamethasone implants allow a sustained release of the agent from a single procedure, preventing fluctuation in drug levels and encouraging compliance.^{54,55} In patients who responded inadequately to ranibizumab, the addition of a dexamethasone implant led to a greater reduction in mean CST after 24 weeks of treatment but did not significantly improve VA.⁵⁶ VA responses varied across lens status; pseudophakic eyes may benefit from combined treatment but phakic eyes may have limited response.⁵⁶

Statement 14: Focal laser and grid laser can be a treatment option with or without anti-VEGF therapy or other combination

In a multicenter trial of 115 eyes with center-involving DME, 47% of patients who received focal or grid laser photocoagulation experienced a $\geq 10\%$ reduction in CST at week 16.⁵⁷ 26 eyes were evaluable at week 32. From weeks 16 to 32, 42% of eyes had an additional $\geq 10\%$ reduction in CST, accompanied by improvements in VA letter score of ≥ 5 letters.⁵⁷

As demonstrated in protocol I, laser treatment in combination with anti-VEGF agents may benefit patients

with center-involving DME. At 2 years, ranibizumab plus either prompt or deferred laser treatment led to the highest proportion of patients achieving ≥ 10 improvements in VA letters, compared with triamcinolone plus prompt laser and sham plus prompt laser (45% to 50% vs 35% vs 25%).⁵⁸

Although panretinal photocoagulation is the mainstay treatment against severe vision loss in proliferative diabetic retinopathy, there is a risk of retina damage, exacerbating DME.⁵⁹ Ranibizumab is non-inferior to panretinal photocoagulation in improving VA after 2 years of treatment and could be an alternative treatment for proliferative diabetic retinopathy for ≤ 2 years.⁵⁹

Statement 15: Pars plana vitrectomy may be performed in patients with vitreomacular traction or epiretinal membrane

Patients with vitreomacular traction tend to respond poorly to anti-VEGF therapy, compared with those without.⁶⁰ Meta-analyses have suggested that pars plana vitrectomy is not superior to other treatment modalities for DME without tractional elements.⁶¹ Therefore, pars plana vitrectomy may be beneficial as a primary treatment for eyes with vitreomacular traction. Pars plana vitrectomy may also benefit patients with concomitant DME and epiretinal membrane, as the presence of epiretinal membrane at baseline is considered a predictor of poor response to anti-VEGF therapy.^{62,63} In a retrospective study of 58 patients with DME, up to 22.4% of patients exhibited epiretinal membrane without vitreous traction at baseline.⁶⁴ Among 19 eyes with concomitant DME and epiretinal membrane, pars plana vitrectomy in combination with epiretinal membrane and internal limiting membrane peeling was effective in improving BCVA and central macular thickness, compared with the preoperative status.⁶⁵

Conclusions

Frequent intraocular injections are barriers to effectively managing DME. Therefore, longer-acting agents are needed. Faricimab, an anti-VEGF agent that targets two pathways (VEGF-A and ANG-2), has demonstrated long-acting efficacy. Brolucizumab, a humanized single-chain variable antibody fragment, has demonstrated long-acting efficacy of up to 16 weeks, allowing longer intervals between treatments. We encourage physicians to include brolucizumab and faricimab in clinical practice for long-term cost savings by reducing the number of visits. However, brolucizumab should be a second-line treatment owing to concerns about retinal vasculitis in the first-line treatment.

Based on clinical response, intervals between treatments can be extended after the loading doses to reduce the treatment burden. Physicians should assess patients' responses to treatment through regular OCT of the macula in the first year. For refractory DME or poor response to anti-VEGF treatment, physicians should consider switching intravitreal anti-VEGF agents. Additionally, switching to steroid therapy or a combination with laser therapy may be beneficial.

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.

Conflicts of interest

NF is a principal investigator of multiple relevant clinical trials, including those mentioned in the article supported by Roche, Bayer, Novartis, Allergan, Ripple, Amgen, Oculis SA, and Chengdu Kanghong Pharm; he has received consulting fees and honoraria from Bayer, Novartis, and Roche. GC has received grant support or contracts from Boehringer Ingelheim and Novartis as well as consulting fees and honoraria from Bayer, Roche, and Zeiss; she was a participant in a board meeting with Boehringer Ingelheim and had a leadership role for a board meeting with Bayer; she has also received stocks from Amirvax. DN has received an honorarium from Roche. TL has received grant support or contracts from Chengdu Kanghong Biotechnology, Novartis, and Roche as well as honoraria from Alcon, Bayer, Boehringer Ingelheim, Novartis, Roche, and Oculis. As editors of the journal, GCMC and TYYL were not involved in the peer

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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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Faricimab to treat neovascular age-related macular degeneration: perspective

Alvin Kwan Ho Kwok, MD (HK), MD (CUHK), PhD (HK), FRCS (UK), FRCOphth (UK), FHKAM (Ophthalmology), PostGrad DipEpidem & Biostat (CUHK), MBBS (HK)
Department of Ophthalmology, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China

Correspondence and reprint requests:

Dr Alvin Kwan Ho Kwok, Department of Ophthalmology, 4/F, Li Shu Fan Block, Hong Kong Sanatorium & Hospital, 2 Village Road, Happy Valley, Hong Kong SAR, China. Email: alvinkhwok@netvigator.com

Abstract

Neovascular age-related macular degeneration (nAMD) is a major cause of vision loss in older adults. Neovascularization is caused by angiogenic mechanisms of the angiopoietin and vascular endothelial growth factor (VEGF) pathways. Standard treatments for nAMD target the VEGF pathway, but the efficacy of single-target anti-VEGF agents is limited by angiopoietin. Some patients may respond inadequately. Faricimab is a bispecific antibody targeting VEGF-A and angiopoietin-2. Its efficacy and safety have been illustrated in the TENAYA, LUCERNE, and TRUCKEE studies. Compared with aflibercept 2 mg, faricimab 6 mg demonstrated rapid best-corrected visual acuity gains and central subfield thickness reductions. A larger proportion of patients did not develop subretinal fluid during the loading phase. Faricimab is well tolerated with a risk-benefit profile comparable to the standard anti-VEGF treatment. Guidelines from the National Institute for Health and Care Excellence and the European Society of Retina Specialists recommend early diagnostic imaging and examinations for timely treatment of nAMD. Faricimab is an efficacious, well-tolerated, and long-acting treatment option for nAMD, with the potential for long-term cost savings.

Key words: Antibodies, bispecific; Faricimab; Intravitreal injections; Visual acuity; Wet macular degeneration

Introduction

Age-related macular degeneration (AMD) is a chorio-retinal vascular disease and the main cause of vision loss in older adults.¹ Most AMD cases start as dry or atrophic AMD, with about 20% progressing to neovascular AMD (nAMD).² Although nAMD is less prevalent, it is associated with severe loss of central vision and accounts for nearly 70% of all vision loss in older adults.^{2,3} The main cause of AMD is age-related macular damage; other risk factors include a family history of AMD and smoking.⁴ In Hong Kong, approximately 500 000 people have AMD, and around 10% of them have nAMD.⁵

Pathophysiology of nAMD

The angiopoietin (Ang)/tyrosine kinase with immunoglobulin and epidermal growth factor homology domain receptor-2 (Tie-2) pathway and vascular endothelial growth factor (VEGF) play an important role in the pathogenesis of nAMD.⁶ Ang-1 activates the Tie-2 receptor on the retinal vessels' endothelial cells to maintain vascular homeostasis. Ang-2 binds to Tie-2 receptors in a similar affinity as Ang-1 but induces the opposite effect: angiogenesis and inflammation.^{6,7} It is important to suppress the Ang-2/Tie-2 pathway in order to stimulate the Ang-1/Tie-2 pathway for vascular homeostasis.

Macular degeneration causes the retina to produce pro-angiogenic VEGF.² Elevated VEGF-A levels promote vascular leakage and neovascularization. These abnormal blood vessels tend to break and form a scar on the macula, causing severe loss of central vision. Increased Ang-2 signaling sensitizes blood vessels to VEGF-A, resulting in

vascular leakage, inflammation, and vascular permeability.⁸ The Ang-2 becomes pro-angiogenic with high levels of VEGF, affecting endothelial cell junction integrity, pericyte drop-off, and angiogenic sprouting.⁷ Patients with nAMD had markedly higher Ang-2 levels, compared with controls (57.39 ± 68.78 pmol/mL vs 10.46 ± 5.90 pg/mL, $p < 0.001$).⁹ High Ang-2 levels can make blood vessels more susceptible to VEGF, thus limiting the efficacy of anti-VEGF agents.⁷ Therefore, targeting Ang-2 may be useful for treating nAMD.

Treatment options for nAMD

Anti-VEGF agents are standard treatment for retinal vascular diseases including nAMD.¹⁰ nAMD is a multifactorial disease with many risk factors and affects the choroidal vessels; neovascularization occurs under the retina and penetrates the photoreceptor layer.^{11,12} Anti-VEGF monotherapies include ranibizumab (anti-VEGF-A), aflibercept (anti-VEGF-A and anti-VEGF-B), and brolucizumab (anti-VEGF-A).^{6,7} Their effectiveness is limited by the role of VEGF in retinal pathogenesis, and some patients may not respond well to standard anti-VEGF agents.^{8,10} Faricimab, a bispecific antibody that inhibits

VEGF-A and Ang-2, is a treatment option for nAMD.^{6,11} We discuss the mechanism of action, clinical evidence, and treatment recommendations of faricimab for nAMD.

Mechanism of action of faricimab

Faricimab is a first-in-class bispecific antibody targeting both VEGF-A and Ang-2 with long-acting effect.^{13,14} Because it targets both VEGF-A and Ang-2, faricimab has long-acting efficacy when treating retinal diseases; additionally, it promotes vascular stability and reduces neovascularization, hyperpermeability, and inflammation, with reduced angiogenesis and less extravasation.¹⁴

Based on results from the phase III TENAYA and LUCERNE studies, the United States Food and Drug Administration and European Medicines Agency approved faricimab for the treatment of nAMD, with a recommended initial dose of 6 mg by intravitreal injection every 4 weeks for the first four doses, followed by the same 6 mg intravitreal dose every 8 to 16 weeks, depending on disease activity.¹⁵⁻¹⁷

Clinical data for faricimab

Table 1 shows clinical studies of faricimab. Faricimab (RG7716) is well tolerated with an overall favorable

Study	Study design	Efficacy	Safety
Chakravarthy et al, ¹⁸ 2017	Phase I, open-label, ascending dose study of intravitreal faricimab	Improvement in best-corrected visual acuity: 7 (0-18) letters for single dose and 7.5 (3-18) letters for multidose; reduction in central subfield thickness: 42 (-101 to 10) μ m for single dose; and -117 (-252 to -7) μ m for multidose	Well tolerated, with an overall favorable safety profile; mild ocular adverse events
Sahni et al, ¹⁹ 2020 (AVENUE)	Phase II, randomized, 36-week, multiple-dose regimen (faricimab vs ranibizumab)	Adjusted mean difference (80% confidence interval) in best-corrected visual acuity was 1.6 (-1.6 to 4.7) letters for faricimab 1.5 mg every 4 weeks ($p=0.52$), -1.6 (-4.9 to 1.7) letters for faricimab 6.0 mg every 8 weeks ($p=0.53$), and -1.5 (-4.6 to 1.6) letters for faricimab 6.0 mg every 8 weeks ($p=0.53$), compared with ranibizumab 0.5 mg every 4 weeks.	No new or unexpected safety events
Cheung et al, ²⁰ 2022; Lai et al, ²¹ 2022; Khanani et al, ²² 2022; Heier et al, ²³ 2022 (TENAYA and LUCERNE)	Phase III, randomized, double-blinded, active comparator-controlled, 112-week studies (faricimab vs aflibercept) in treatment-naïve patients	Adjusted mean change (95% confidence interval) in vision gain in year 1 was 5.8 (4.6-7.1) letters for faricimab and 5.1 (3.9-6.4) letters for aflibercept (in TENAYA) and 6.6 (5.3-7.8) letter for faricimab and 6.6 (5.3-7.8) letters for aflibercept (in LUCERNE). >50% of patients were maintained on faricimab every 16 weeks after the loading phase throughout the year. More faricimab-treated patients had no subretinal and/or retinal fluid than aflibercept-treated patients. Mean vision gains in year 2 was 3.7 letters for faricimab and 3.3 letters for aflibercept (in TENAYA) and 5.0 letters for faricimab and 5.2 letters for aflibercept (in LUCERNE). Reductions in central subfield thickness in year 2 was -146.5 μ m for faricimab and -146.2 μ m for aflibercept (in TENAYA) and -150.3 μ m for faricimab and -141.6 μ m for aflibercept (in LUCERNE). Median number of injections was 10 for faricimab every 16 weeks and 15 for aflibercept every 8 weeks.	Rate of ocular adverse events in year 1 was 36.3% for faricimab and 38.1% for aflibercept (in TENAYA) and 40.2% for faricimab and 36.2% for aflibercept (in LUCERNE). Faricimab had lower rates of intraocular inflammation; no cases of retinal vasculitis or occlusive retinal vasculitis were reported. In year 2, faricimab was well tolerated and had a favorable risk-benefit profile; there were no reported cases of retinal vasculitis or intraocular inflammation associated with retinal occlusion.
Sheth et al, ²⁵ 2022 (TRUCKEE)	Real-world efficacy and safety	In 174 patients who switched from aflibercept to faricimab after 44.8 days, there were improvements in Early Treatment Diabetic Retinopathy Study letters of +1.1 letters, reduction in central subfield thickness of -25.7 μ m, and reduction in pigment epithelial detachment height of -27.1 μ m	Endophthalmitis (n=1), intraocular inflammation (n=0), retinal vasculitis (n=0), retinal artery occlusions (n=0)

safety profile, while improving best-corrected visual acuity (BCVA) and anatomic parameters.^{18,19} The phase II AVENUE study confirmed faricimab's safety profile and efficacy to be comparable to monthly ranibizumab intravitreal injections.¹⁹

In phase III, randomized, double-blinded, aflibercept-controlled, 112-week studies (TENAYA and LUCERNE) [Figure],²⁰⁻²³ patients in the aflibercept (control) group received 3-monthly loading doses before being assigned to an 8-weekly dosing interval, whereas patients in the faricimab (experimental) group received 4-monthly loading doses (at weeks 0, 4, 8, and 12), followed by sham procedures at weeks 16 and 20. Patients were subsequently assigned to 16-weekly, 12-weekly, or 8-weekly dosing intervals based on disease activity at weeks 20 and 24. Faricimab-treated patients without active disease (based on optical coherence tomography (OCT), visual acuity, and clinical

examination) at weeks 20 and 24 could immediately extend from 4-weekly to 16-weekly dosing. In the second year of treatment, faricimab was dosed according to a personalized treatment interval, which can be maintained, extended to up to 16-weekly dosing, or reduced to 8-weekly dosing, depending on criteria for central subfield thickness (CST), BCVA, or macular hemorrhage. If any of these criteria is met, the treatment interval is reduced by 4 weeks, and if at least two of these criteria are met, the treatment interval is reduced by 8 weeks.

During the loading phase (first 12 weeks), more faricimab-treated patients experienced no subretinal fluid and/or intraretinal fluid than aflibercept-treated patients (77% vs 67%, $p < 0.05$).²⁰ First-year data from both TENAYA and LUCERNE studies showed that faricimab-treated patients were non-inferior to aflibercept-treated patients in terms of BCVA change from baseline.²⁰ In the TENAYA trial,

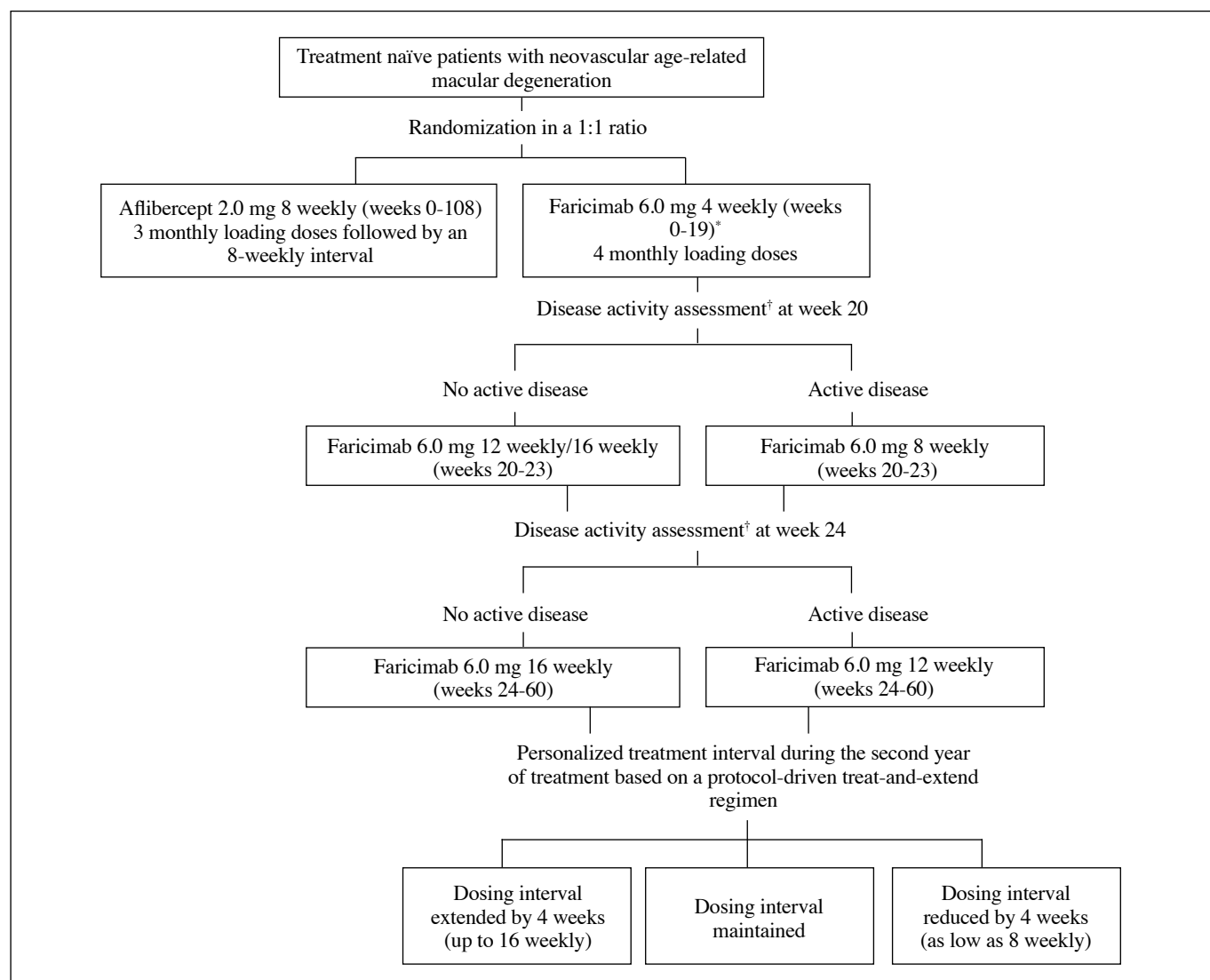


Figure. Study design for the TENAYA and LUCERNE studies²⁰⁻²²

* The four monthly doses were administered at weeks 0, 4, 8, and 12. At weeks 16 and 20, a sham procedure was administered

† Best-corrected visual acuity loss ≥ 5 letters (vs mean) or ≥ 10 letters (vs highest recorded); or central subfield thickness increase ≥ 50 μm (vs mean) or ≥ 75 μm (vs highest recorded); or presence of new macular hemorrhage.

the adjusted mean change was 5.8 letters (95% confidence interval [CI]=4.6-7.1) for faricimab and 5.1 letters (95% CI=3.9-6.4) for aflibercept.²² In the LUCERNE trial, the adjusted mean change was 6.6 letters for both faricimab (95% CI=5.3-7.8) and aflibercept (95% CI=5.3-7.8).²³ The second-year data showed that faricimab up to 16-weekly dosing (3 injections) was comparable to aflibercept 8-weekly dosing (6 injections) in terms of vision improvements.²² In the TENAYA study, the mean vision gain from baseline was +3.7 eye chart letters for faricimab and +3.3 letters for aflibercept.²² In the LUCERNE trial, the mean vision gain from baseline was +5.0 letters for faricimab and +5.2 letters for aflibercept.²² By week 108, patients on faricimab up to 16-weekly dosing had a lower median number of injections than patients on aflibercept 8-weekly dosing (10 vs 15).²²

Patients on faricimab (up to 16-weekly dosing) had rapid meaningful CST reductions in the initial dosing phase, and these were sustained throughout the maintenance phase.²² Similarly, approximately 45% of patients treated with faricimab 16-weekly dosing exhibited an early reduction in CST that was stable throughout the maintenance phase, albeit with fewer injections.²² Both the TENAYA and LUCERNE studies showed reduction in CST: -146.5 μ m with faricimab up to 16-weekly dosing versus -146.2 μ m with aflibercept 8-weekly dosing, and -150.3 μ m with faricimab up to 16-weekly dosing versus -141.6 μ m with aflibercept 8-weekly dosing, respectively.²²

At week 112, faricimab showed long-acting disease control: maintenance of vision gain, CST reduction, and BCVA improvement.²² In the TENAYA study, the proportion of patients on faricimab 16-weekly dosing increased from 45.7% at week 48 to 59.0% at week 112.²² In the LUCERNE study, the proportion of patients on faricimab 16-weekly dosing increased from 44.9% at week 48 to 66.9% at week 112. The proportion of patients on extended dosing intervals (12-weekly and 16-weekly) remained similar over years 1 and 2 in both trials.²² Maintenance of vision gain can be attributed to the vascular stability achieved by targeting both the VEGF-A and Ang-2 pathways.⁷ The TENAYA and LUCERNE studies found promising results for longer intervals between dosing, highlighting the potential for individualized treatment regimens and reduced treatment burden.²¹ By week 108, the median number of injections was 10 for faricimab and 15 for aflibercept. In personalized treatment interval by week 60, the median number of injections was 3 for faricimab up to 16-weekly dosing and 6 for aflibercept 8-weekly dosing.²²

Faricimab is well tolerated with a favorable risk-benefit profile. The TENAYA and LUCERNE trials showed that faricimab and aflibercept had acceptable and comparable safety profiles during the first and second years of treatment.^{21,22} The rates of intraocular inflammation were low, and no cases of retinal vasculitis or occlusive retinal vasculitis were reported.^{21,22} The Hong Kong Retina Expert Panel provides recommendations for treat-and-extend regimen for managing nAMD.²⁴

Real-world data for faricimab

The TRUCKEE study investigated the outcome of intravitreal faricimab in treatment-naïve patients and patients with persistent disease activity.²⁵ Patients who switched from aflibercept to faricimab were followed up after a mean of 44.8 days; all had better visual acuity, reduction in CST, and pigment epithelial detachments. There were no cases of intraocular inflammation, retinal vasculitis, or retinal artery occlusions after the use of faricimab.

Using faricimab to treat nAMD in clinical practice

Assessment and diagnosis

Early diagnosis and timely treatment of nAMD are crucial to prevent vision deterioration.²⁶ Diagnosis may be delayed because of lack of symptoms and unawareness of visual changes.²⁶ nAMD should be suspected in patients with distorted or reduced vision, particularly when there are other related risk factors.^{4,27} Various guidelines recommend that older patients aged ≥ 50 years with visual problems should undergo eye investigations such as the Amsler grid and visual acuity tests.^{4,26,28,29} Although both tests are readily accessible, operators should be aware that sensitivity can vary for the Amsler grid and is not specified for visual acuity tests.³⁰ OCT or fundus fluorescein angiography should be considered.^{1,4} OCT can detect intra- and sub-retinal fluid and is supplementary to fundus fluorescein angiography,³⁰ which should be performed if OCT does not indicate any abnormalities but visual acuity is reduced.⁴

Treatment and monitoring

Intravitreal injection of faricimab 6 mg every 4 weeks for four doses should be used to treat nAMD. Treatment response and disease status should be assessed using OCT and visual acuity tests.¹⁶ Subsequent doses of faricimab can be given at longer intervals of every 8 to 16 weeks.¹⁵ Patients without active disease by weeks 20 and 24 can immediately switch from 4-weekly to 16-weekly dosing.^{20,21}

Both the National Institute for Health and Care Excellence and the Australian Pharmaceutical Benefits Advisory Committee recommend faricimab for nAMD.^{11,31} Faricimab is registered for use in Hong Kong.³² Faricimab should be administered if the patient has a BCVA between 6/12 and 6/96, no permanent structural damage to the central fovea, a lesion with the greatest linear dimension of ≤ 12 -disc areas, and signs of recent disease progression.¹¹ Faricimab has

Table 2. Annual dosage of faricimab and aflibercept for neovascular age-related macular degeneration²²

Anti-vascular endothelial growth factor agents	Median No. of injections throughout the 2 years	Median No. of injections in the second year of treatment
Faricimab 6 mg	10	3
Aflibercept 2 mg	15	6

comparable efficacy and safety to aflibercept.³¹ Faricimab 6 mg and aflibercept 2 mg are equally cost-effective for the treatment of nAMD.³¹ Cost-effectiveness may vary according to the study setting and/or design. The TENAYA and LUCERNE studies demonstrated that treatment with faricimab necessitated a lower median number of injections in the first year than treatment with aflibercept (Table 2).²² More than 78% of patients receiving faricimab could be dosed once every 12 weeks or at longer intervals.²⁵

Conclusions

The VEGF and Ang-2 pathways play an important role in the pathogenesis of nAMD. Faricimab is a novel bispecific antibody that inhibits both the VEGF and Ang-2 pathways. Clinical and real-world data suggest that faricimab treats nAMD as effectively as aflibercept with a similar safety profile but requires fewer injections. Therefore, faricimab offers potential long-term cost savings by reducing the number of medical visits and hence treatment burden.

Contributors

The author designed the study, acquired the data, analyzed

the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. The author had full access to the data, contributed to the study, approved the final version for publication, and takes responsibility for its accuracy and integrity.

Conflicts of interest

Roche paid AKHK honorarium as the chairman of the College of Ophthalmologists of Hong Kong Annual General Meeting in 2022 and an advisor at the Hong Kong DME advisory board meeting.

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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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Nutraceuticals for infants with retinopathy of prematurity: perspective

Anakin Chu Kwan Lai¹, Christie Nicole Lun², Connie Hong Yee Lai², Nicholas Siu Kay Fung¹, Amy Cheuk Yin Lo¹

¹Department of Ophthalmology, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

²Grantham Hospital, Hospital Authority, Hong Kong SAR, China

Correspondence and reprint requests:

Amy Cheuk Yin Lo, Department of Ophthalmology, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China. Email: amylo@hku.hk

Abstract

Retinopathy of prematurity (ROP) is one of the most common causes of childhood blindness worldwide. Its prevalence is rising as more premature infants are surviving owing to advances in neonatal care. The current treatments for ROP are invasive and may increase the risk of future eye complications. Nutraceuticals (dietary oils, carotenoids, and vitamin supplements) are generally safe for use in children without detrimental adverse effects. Research has demonstrated nutraceuticals' anti-angiogenesis properties and their potential to protect against ROP. Dietary oils suppress inflammation and neovascularization in ROP models when administered intravenously. Carotenoids, such as lutein, promote retinal revascularization in mice. Vitamin A, C, and E supplements are unable to prevent ROP pathogenesis, despite well-documented antioxidative effects. The discrepancy between laboratory and clinical trial results may be due to differences in the dosage that can affect the eye, the outcome measurements used, and the presence of confounders in clinical trials. Future studies should investigate the short- and long-term effects of nutraceuticals on infants' vision.

Key words: Blindness; Child; Hyperoxia; Hypoxia; Retinal neovascularization

Introduction

Childhood blindness accounts for approximately 4% of all blindness cases; children with blindness, on average, live without vision 40 years longer than adults.¹ Retinopathy of prematurity (ROP) is a common cause of childhood blindness worldwide, responsible for 14% of all childhood blindness cases.^{2,3} The number of ROP cases increases as supplemental oxygen therapy increases the survival rate of premature babies.⁴ The relative hypoxia following oxygen therapy causes neovascularization and blindness in ROP. A Swedish study reported that up to 73% of premature infants have ROP.⁵ In a Hong Kong hospital, 16.9% of premature infants are diagnosed with ROP in 2013.⁶ ROP as a cause of blindness is expected to increase as neonatal care advances and more premature infants survive.⁷

The current mainstay treatments for ROP are cryotherapy, laser therapy, and intravitreal injection of anti-vascular endothelial growth factor (VEGF).⁸ However, these treatments are associated with rare ocular and systemic adverse effects including cataracts, corneal burns, and delayed neurodevelopment.⁹⁻¹³ A noninvasive, high-efficacy treatment for ROP has yet to be developed.

Nutraceuticals in ROP

Nutraceuticals are natural substances with health benefits in both in vivo and in vitro ROP models.¹⁴ They are widely used in cardiovascular diseases for their antioxidative and anti-inflammatory responses.¹⁵ Nutraceuticals may be less likely to trigger adverse effects in children and may promote

Table. Clinical effects of nutraceuticals on infants with retinopathy of prematurity						
Study	Study design	Sample size	Compound used	Route	Dosage	Outcome
Pawlik et al, ²⁶ 2011	Cohort study	68 (treatment group: 44)	20% clinoleic: 50% soybean and olive oil emulsion; 10% omegaven: 50% fish-oil emulsion	Intravenous	Birth weight <1000 g: omegaven 0.15 g + clinoleic 0.35 g Birth weight >1000 g: omegaven 0.35 g + clinoleic 0.65 g	Reduced ROP incidence Reduced risk of laser therapy for infants
Beken et al, ²⁹ 2014	RCT	80 (treatment group: 40)	20% intralipid: soybean oil 200 g/dL 20% SMOFlipid: soybean oil 60 g/dL, MCT 60 g/dL, olive oil 50 g/dL, fish oil 30 g/dL	Intravenous	Birthweight <1000g: 0.5 g lipids per kg Birthweight >1000g: 1.0 g lipids per kg	Reduced ROP incidence
Najm et al, ²⁵ 2017	RCT	78 (treatment group: 41)	Lipid solution (clinoleic or SMOFlipid)	Enteral	6-12 h after birth: 1 g/kg/d with daily increases up to 2 g/kg/d	No difference in ROP incidence
Bernabe-Garcia et al, ³¹ 2019	RCT	110 (treatment group: 55)	Docosahexaenoic acid	Enteral	75 mg/kg/d	No difference in ROP incidence Reduced risk of stage-3 ROP
Tu et al, ³⁰ 2020	RCT	396 (treatment group: 193)	20% Lipovenoes medium-chain triglycerides: 50% soybean oil SMOFlipid: 30% soybean oil, 25% olive oil, and 15% fish oil	Intravenous	3 g/kg/d	Reduced ROP incidence Reduced the need for anti-VEGF treatment
Hellstrom et al, ³² 2021	RCT	206 (treatment group: 101)	Enteral oil	Enteral	Arachidonic acid 100 mg/kg/d, docosahexaenoic acid 50 mg/kg/d	No difference in ROP incidence Lowered the risk of severe ROP by 50%
Romagnoli et al, ⁴⁴ 2011	RCT	63 (treatment group: 31)	Lutein + zeaxanthin	Enteral	Lutein 0.5 mg/kg/d Zeaxanthin 0.02 mg/kg/d	No difference in ROP incidence
Dani et al, ⁴² 2012	RCT	114 (treatment group: 58)	Lutein + zeaxanthin	Enteral	Lutein 0.14 mg daily Zeaxanthin 0.006 mg daily	No difference in ROP incidence
Rubin et al, ¹⁹ 2012	RCT	183 (treatment group: 92)	Lutein + zeaxanthin + lycopene + beta-carotene	Enteral	Lutein 211 µg Lycopene 143 µg Beta-carotene 219 µg	No difference in ROP incidence Fewer infants in treatment group developed ROP Significantly greater sensitivity response in rod photoreceptors
Manzoni et al, ⁴³ 2013	RCT	229 (treatment group: 113)	Lutein + zeaxanthin	Enteral	Lutein 0.14 mg daily Zeaxanthin 0.006mg daily	No difference in ROP incidence
Mactier et al, ⁴⁵ 2012	RCT	89 (treatment group: 42)	Vitamin A	Intramuscular	10000 IU 3 times a week from day 2 for a minimum of 2 weeks or the start of oral feeding	No difference in ROP incidence or severity Weak correlation between retinal sensitivity and total vitamin A intake per kg over the first 4 weeks of life
Sun et al, ⁴⁹ 2020	RCT	262 (treatment group: 132)	Vitamin A	Enteric	1500 IU/day	Reduced incidence of ROP (mild, type I, and type II)
Darlow et al, ⁵⁵ 2005	RCT	119 (low dose throughout: 40; low dose for 10 days then high dose: 40; high dose throughout: 39)	Vitamin C	Enteric	Additional 20 mg/kg/day	No difference in ROP incidence or severity
Romero-Maldonado et al, ⁴⁸ 2021	RCT	90 (treatment group: 48)	Vitamin E	Enteric	12.5 IU every 12 h from 72 h after birth to 28 days	Reduced incidence of ROP Reduced severity of ROP

Abbreviations: RCT=randomized controlled trial, ROP=retinopathy of prematurity, and VEGF=vascular endothelial growth factor

long-term health.^{16,17} For example, prolonged carotenoid consumption reduces the risks of atherosclerosis and macular degeneration.^{18,19} We aim to review clinical studies of nutraceuticals (dietary oils, carotenoids, and vitamin supplements) for managing ROP (Table).

Dietary oils

Dietary oils are mainly found in fatty fish (salmon and trout) and plant-based oils (soybean oil).²⁰ They contain long-chain polyunsaturated fatty acids (LCPUFAs), including arachidonic acid (AA) and docosahexaenoic acid

(DHA), which are important for infants' neurological and visual development. Indeed, they are given to premature infants for nutrition and immunomodulation.¹⁴ LCPUFAs downregulate tumor necrosis factor α and inhibit cell proliferation, suppressing inflammatory and oxidative responses and thus reducing neovascularization in ROP models.²¹⁻²³ Premature infants have lower serum AA levels,²⁴ so additional LCPUFAs might be therapeutic in ROP. However, not all clinical trials have observed a significant reduction in the incidence of ROP after treatment with enteral LCPUFAs.²⁵

The main source of lipids for premature infants is fat emulsions that do not contain DHA.²⁶ Therefore, supplementary DHA in breast milk is recommended to prevent ROP.^{27,28} However, LCPUFAs are effective to reduce both the incidence of ROP and the need for laser or anti-VEGF treatment only when administered intravenously. When LCPUFAs are given enterally, although the severity of ROP reduces, the incidence does not.^{26,29-32} This discrepancy implies that premature infants with poor gut development cannot effectively digest LCPUFAs.³³ As the intravenous route is invasive and associated with risks of bruising, inflammation, and infection, different routes of administration for LCPUFA should be considered.

The type of LCPUFA given to premature infants affects the therapeutic effect on ROP. Interactions between different nutraceuticals may be disturbed by the supplementation of certain LCPUFAs.³⁴ Simple administration of DHA and AA has a limited effect on the incidence of ROP.^{31,32} Further investigation into the optimum dosage, formulation, and route of administration is required before LCPUFAs can be used therapeutically.

Carotenoids

Carotenoids are pigments found mainly in dark green vegetables and egg yolk. They are obtained exclusively from diet and are essential to the formation of macular pigment.^{35,36} Lutein, in particular, reduces inflammation by lowering the number of glial fibrillary acidic protein and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling-positive apoptotic cells after retinal hypoxia in both in vitro and in vivo mouse models.^{37,38} In the human body, lutein is found mostly in the macula and the lens, with anti-oxidative effects. It protects against cataracts and age-related macular degeneration by blocking blue light.^{8,39} It is 'generally regarded as safe' by the United States Food and Drug Administration.⁴⁰

Lutein promotes retinal revascularization and reduces vascular leakage in oxygen-induced retinopathy mouse models,⁴¹ but no such effects have been observed in clinical trials. Adding lutein to human milk has no significant protective effect against ROP development.^{19,42-44} However, in one study, only 8% of mild ROP infants developed severe ROP after treatment with supplementary lutein, compared to 28% in controls; infants with supplementary lutein have significantly greater rod photoreceptor sensitivity

responses.¹⁹

Discrepancy between laboratory and clinical data may be related to the absorption of lutein supplements. Lutein is lipophilic, so effective enteral absorption is difficult, especially in premature infants because the transfer of lipophilic nutrients occurs during the later weeks of pregnancy.¹⁹ As a result of poor absorption, the plasma lutein levels are not high enough to exert a neuro-protective and revascularization effect on the retina. Dissolving lutein in olive oil to increase its absorption and bioavailability has been suggested.¹⁴

Vitamin supplements

Vitamins A, C, and E all have antioxidative effects. Vitamin A is found mainly in leafy green vegetables, fish oils, milk, and eggs; vitamin C in citrus fruits and bell peppers; and vitamin E in nuts and seeds. Vitamin A (retinol) increases the availability of rhodopsin for phototransduction, which reduces the demand for oxygen in photoreceptor development;⁴⁵ vitamin C exerts its antioxidant effect by electron donation and transfer;⁴⁶ and vitamin E inhibits the production of new oxygen radicals while neutralizing existing ones.⁴⁷ They potentially protect against oxidative damage in ROP.

Both vitamins A and E are used to reduce the risk of developing respiratory complications such as bronchopulmonary dysplasia and respiratory distress syndrome. Infants with better lung function have less need for high-concentration oxygen therapy and are therefore less exposed to the oxidative damage that causes ROP.^{45,48,49} However, vitamin A's protective effect is only evident when it is administered orally.⁴⁹ Intramuscular injection of vitamin A did not reduce ROP incidence.⁴⁵ The plasma level of vitamin A does not correlate with body stores, making it difficult to establish an optimal dose.⁵⁰ Vitamin E protects polyunsaturated fatty acid from lipoperoxidation, which is involved in ROP pathogenesis.^{51,52} Enteric supplementation of vitamin E reduces the risk of ROP in very low-birthweight infants by 60%.⁴⁸ However, using vitamin E for ROP prophylaxis may increase the risk of intraventricular hemorrhage during the early days of prematurity.⁵²

Vitamin C (ascorbic acid) is an antioxidant and has pro-oxidative effect.^{53,54} However, existing clinical studies have not demonstrated any significant reduction in either the incidence or severity of ROP after administration of supplementary ascorbic acid.⁵⁵ In fact, excessively high plasma levels of ascorbic acid may increase mortality in the first days of life.⁵⁶ Therefore, vitamin C supplementation is not suitable for the prevention of ROP.

Discrepancy between laboratory and clinical evidence

Laboratory studies have demonstrated the benefits of nutraceuticals including anti-angiogenesis, suppression of endothelial growth factor secretion, and reduction of neovascular areas. However, only a few clinical trials

have shown a reduction in the incidence of ROP after administering nutraceuticals.

The dose of nutraceuticals that can reach the eye may be different. Oral, intravitreal, and intraperitoneal administrations are typical in laboratory studies, but oral and intravenous routes are typically used in clinical trials. Different administration routes result in different metabolism and affect the amount of nutraceutical that reaches the retina. Moreover, premature infants' underdeveloped feeding and absorption may reduce the plasma level and efficacy of nutraceuticals. The dosage given in clinical trials is also limited by the unknown effects of nutraceuticals on the infant's overall health. Clinical trials start at a low dose, which may not be enough to be effective. Therefore, the level of nutraceuticals that can induce an effect in clinical trials is difficult to standardize and measure.

Parameters used to quantify outcomes are different. Laboratory studies usually measure the reduction in angiogenesis and inflammation, the suppression of VEGF and angiotensin II, and the reduction in neovascularization area, whereas clinical studies mainly measure ROP incidence and severity. The effects shown in laboratory studies are probably insufficient to reduce the incidence or severity of ROP in clinical studies.

There are confounders in clinical trials. Premature infants differ in birthweight, degree of prematurity, comorbidities, genetic predisposition, and/or quality of care. These factors, which are more standardized in laboratory studies, may affect the efficacy of nutraceuticals in reducing ROP incidence.

Future directions

There is sufficient laboratory-based evidence to confirm that the antioxidative and anti-inflammatory effects of nutraceuticals are effective in preventing ROP. However, clinical trials of nutraceuticals for premature infants to prevent ROP are limited. Most clinical trials investigate the effects of dietary oils, carotenoids, and vitamin supplements, but the effects of flavonoids and herbal formula are less studied. Flavonoids, found in green tea extracts, inhibit angiogenesis and suppress matrix metalloproteinase-2 activity in rats.⁵⁷ They are found in bilberries and have antioxidative properties, which help to reduce lipid peroxidation and prevent cell apoptosis.^{58,59} Although

the mechanisms of action behind most herbs are not well understood, a few standardized herbal formulae such as Guibi-tang and Samul-tang reportedly protect against retinal neovascularization in murine oxygen-induced retinopathy models.^{60,61}

The long-term effects of nutraceuticals on visual acuity and neurological development of infants with ROP should be monitored. The interaction effects between nutraceuticals and existing treatments such as anti-VEGF are unclear. For example, vitamin E reduces LCPUFA lipoperoxidation and potentially demonstrates a synergistic effect when given adjunctively with anti-VEGF therapy. More basic and clinical studies on short- and long-term effects of nutraceuticals are warranted.

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.

Conflicts of interest

As editors of the journal, CHYL and ACYL were not involved in the peer review process. Other 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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Different routes of steroidal administration for non-infectious uveitis: perspective

Ho Lam Wong¹; Alvin Kwan Ho Kwok,² MBBS (HK), MD (HK), MD (CUHK), PhD (HK), PDip Epidemiology and Biostatistics (CUHK), FRCSEd, FCSHK, FCOphth HK, FRCOphth, FHKAM (Ophthalmology)

¹Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong SAR, China

²Department of Ophthalmology, Hong Kong Sanatorium Hospital, Hong Kong SAR, China

Correspondence and reprint requests:

Dr Alvin Kwan Ho Kwok, Department of Ophthalmology, Hong Kong Sanatorium Hospital, 4/F, Li Shu Fan Block, 2 Village Road, Happy Valley, Hong Kong SAR, China. Email: alvinkwok@hksh.com

Abstract

Uveitis is inflammation of the iris, ciliary body, and/or choroid and accounts for 10% to 15% of legal blindness cases in Europe and the United States, and particularly affects working-age people. Systemic steroids are the first-line treatment for intermediate and posterior non-infectious uveitis (NIU), whereas topical steroids are reserved for anterior uveitis. However, systemic steroids can lead to complications such as hypertension, diabetes, and secondary infection. Local use of steroids can suppress intraocular inflammation and cystic macular edema with fewer systemic risks. Intravitreal dexamethasone, fluocinolone acetonide, and/or triamcinolone acetonide implants can improve visual acuity and reduce central retinal thickness. Additionally, suprachoroidal injections of triamcinolone acetonide can reduce central subfield thickness in patients with uveitis. Subtenon injections of triamcinolone acetonide reduce central macular thickness more than periocular injections. Systemic intravenous methylprednisolone pulses can rapidly suppress uveal tract inflammation. Topical use of dexamethasone-cyclodextrin nanoparticles can penetrate the anterior segment to resolve vitritis and macular edema, but cataract progression, elevated intraocular pressure, and deterioration of glaucoma may still occur. During the COVID-19 pandemic, uveitis specialists preferred to use local corticosteroids

rather than systemic immunosuppressants and biologics. They advocated dose tapering in patients taking high-dose corticosteroids to reduce their susceptibility to viral infection. NIU is increasingly managed with local steroids to reduce infection risk. This article highlights different routes for steroidal treatments of NIU, including intravitreal, suprachoroidal, periocular, systemic, and topical routes. It also discusses how NIU was managed during the COVID-19 pandemic, specifically addressing the use of immunosuppressants and biologics.

Key words: Intravitreal injections; Steroids; Uveitis, intermediate; Uveitis, posterior

Introduction

Uveitis refers to inflammation of the uveal tract, which includes the anterior ciliary body and iris (anterior uveitis), posterior ciliary body and vitreous humor (intermediate uveitis), and retina and choroid (posterior uveitis). Panuveitis refers to inflammation of all anterior, intermediate, and posterior structures involving the retina, sclera, and optic nerve. Non-infectious uveitis (NIU) can be associated with systemic diseases (such as juvenile idiopathic arthritis, sarcoidosis, and Behcet's disease) or can be an isolated ocular disease (such as birdshot chorioretinopathy). Uveitis causes 10% to 15% of legal blindness cases in Europe and the United States, with a prevalence of 121 per 100 000, and particularly affects working-age people.¹ It adversely affects patients' quality of life and can lead to cataracts,

inflammatory vitreous haze, cystoid macular edema (CME), and blindness.²

Local corticosteroids are the first-line treatment for anterior uveitis but are contraindicated in patients with raised intraocular pressure (IOP) secondary to steroid use. Systemic corticosteroids are administered for first-episode intermediate and posterior NIU and panuveitis, bilateral NIU, NIU resistant to local therapy, and NIU associated with systemic disorders; oral prednisolone is the first-line treatment.³ Systemic immunosuppressants (such as methotrexate, azathioprine, and mycophenolate mofetil) are used in patients with NIU refractory to steroids,⁴ when steroids are poorly tolerated, or in young patients with anticipated long-term topical steroid use and risk of cataract progression. Biologics (such as adalimumab, infliximab, and tocilizumab) are increasingly used to treat NIU.⁵ Subcutaneous adalimumab has a longer time to treatment failure than a placebo in treating intermediate or posterior uveitis.⁶ Adalimumab injections lower the risk of uveitis flare or visual loss upon steroid withdrawal in patients with NIU.⁶

Posterior uveitis is sight threatening. Topical steroids have low bioavailability and do not effectively deliver the active ingredient to the posterior segment.⁷ Different routes of steroid delivery have been developed to minimize the adverse effects of systemic steroid use, such as immunosuppression, hypertension, central obesity, and diabetes mellitus. This article highlights different routes for steroidal treatments

of NIU, including intravitreal, suprachoroidal, periocular, systemic, and topical routes (**Figure 1**). It also discusses how NIU was managed during the COVID-19 pandemic, specifically addressing the use of immunosuppressants and biologics.

Intravitreal injection

The intravitreal route refers to administering drugs into the vitreous humor, usually at the superotemporal or inferotemporal sites. Intravitreal injection is contraindicated in patients with an active ocular infection. Caution should be taken in patients with prior trabeculectomy or a glaucoma drainage device to avoid injecting into the bleb or shunt. Injecting steroids locally, including through the intravitreal route, can minimize systemic side effects and are particularly suitable for patients with peptic ulcers or poor liver or renal function. Dexamethasone, fluocinolone acetonide, and triamcinolone acetonide all can improve visual outcomes and reduce the severity of uveitic macular edema (UME) [**Table 1**].

Dexamethasone

The corticosteroid dexamethasone blocks the cascading inflammatory mechanism and inhibits the release of cytokines or chemotactic proteins.⁸ It is available in a liquid form (4 mg/mL) and is also used in a polymeric slow-release delivery system or as an intravitreal implant because of its low solubility. The intravitreal implant Ozurdex (dexamethasone 0.7 mg; Allergan, AbbVie, North Chicago [IL], USA) has been approved to treat retinal vein

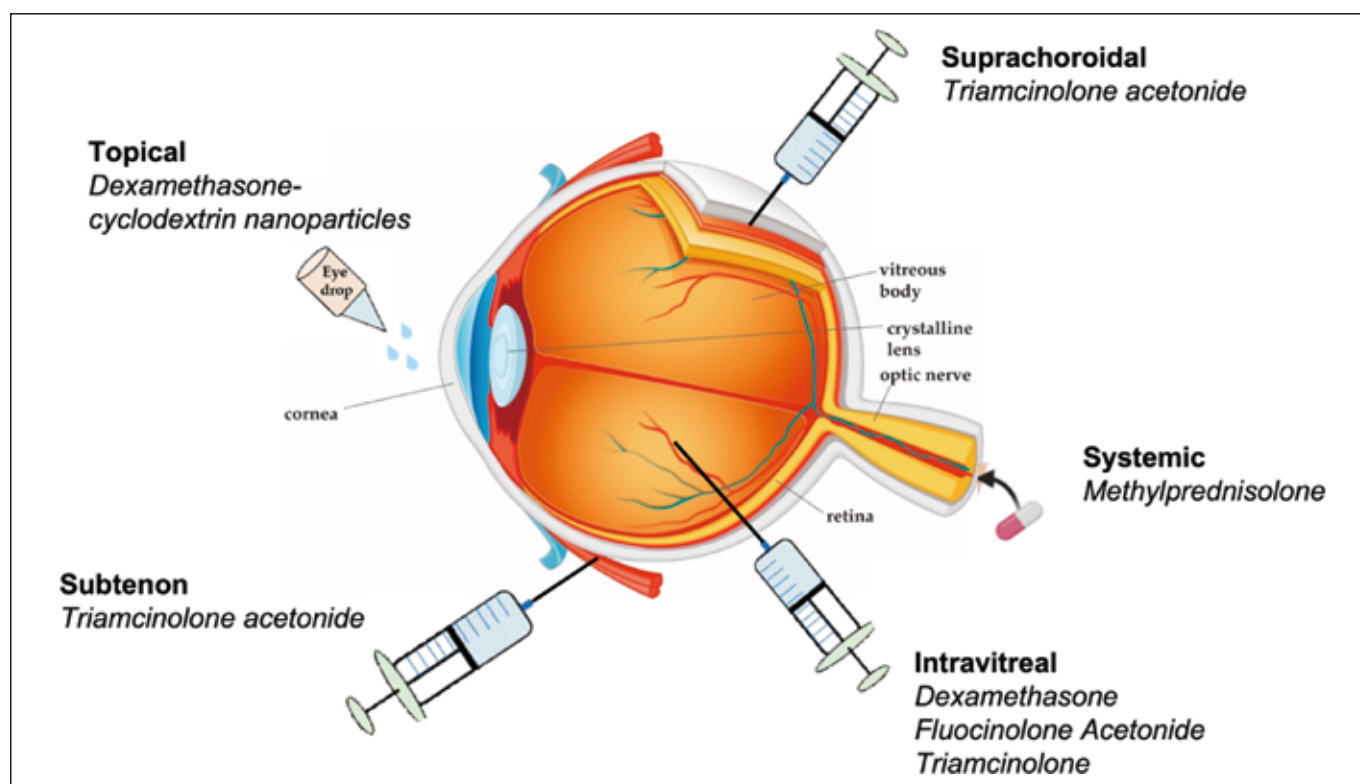


Figure 1. Schematic diagram showing the different routes of steroidal administration for non-infectious uveitis.

Table 1. Studies of intravitreal steroid injection for non-infectious uveitis			
Study	Study type	Patient characteristics	Main results
Dexamethasone			
Bodaghi et al, ¹⁰ 2022	Prospective	245 patients with posterior NIU received 0.7 mg dexamethasone intravitreal implants were evaluated at months 2, 6, and 18.	20.5% and 25% of patients gained >15 letters at months 2 and 6, respectively. 50.0% of patients did not require alternative treatment or retreatment. CRT reduced by 27.4%, 18.5%, and 16.4% at months 2, 6, and 18, respectively.
Tsang et al, ¹² 2017	Retrospective	15 patients with posterior NIU and CME received a single 0.7 mg dexamethasone intravitreal implant and were followed up for 12 months.	At month 3, 91.4% of patients had CRT reduction from 590 to 370 μ m ($p<0.001$) and 80% of patients had visual acuity improvement from logMAR 0.614 to 0.35 ($p=0.002$).
Zeng et al, ¹³ 2022	Retrospective	77 patients with NIU received dexamethasone intravitreal implants and were assessed at week 1 and months 1, 3, and 6.	Respectively at week 1 and months 1, 3, and 6, the mean BCVA improved to logMAR 0.245, 0.437, 0.380, and 0.316, and the CRT decreased from 649.1 μ m to 340.9, 287.9, 357.2, and 387.1 μ m.
Hasanreisoglu et al, ¹¹ 2019	Retrospective	44 patients with NIU with CME or vitreous haze and intraocular inflammation received intravitreal dexamethasone implants and were followed up for 20 months.	Respectively at months 1, 3, and 6, the mean BCVA improved from logMAR 0.55 to logMAR 0.38, 0.32, and 0.35, and the mean CRT decreased to 288, 311, and 302 μ m. Vitreous haze decreased until month 6.
Nobre-Cardoso et al, ¹⁴ 2017	Retrospective	31 patients with NIU and persistent CME resistant to systemic immunosuppression received dexamethasone intravitreal implants.	The mean BCVA improved from 0.74 to 0.84 logMAR at month 1 but started to deteriorate at month 6 in 56.5% of eyes. CRT decreased at month 1 but increased at month 6 in almost all eyes.
Fluocinolone acetonide			
Tomkins-Netzer et al, ²¹ 2015	Randomized controlled trials	108 patients with uveitic macular edema were randomly assigned to receive systemic immunosuppression or an intravitreal FA 0.59 mg implant and were followed up for 2 years.	In the implant group, 71% of the eyes had improved macular edema and 60% had resolved edema. The decrease of macular thickness was more in the implant group than in the systemic therapy group (180 vs 109 μ m, $p=0.04$). The mean BCVA improved by 10 letters in both groups.
Tomkins-Netzer et al, ²³ 2021	Randomized controlled trials	177 patients with uveitic macular edema were randomly assigned to receive systemic immunosuppression or an intravitreal FA 0.59 mg implant and were followed up for 7 years.	Macular edema resolved in 94% of eyes after a median time of 1.09 years. 43% of eyes had relapsed macular edema by year 7, which was associated with central macular thickness (hazard ratio=2.02) and being Black (hazard ratio=1.80). Eyes with resolved macular edema gained 6.24 letters more than those with relapsed macular edema ($p<0.001$).
Kempen et al, ²² 2011	Randomized controlled parallel superiority trial	255 patients with bilateral NIU (intermediate, posterior, or panuveitis) were randomly assigned to receive systemic corticosteroids plus immunosuppression or an FA implant and were monitored for 24 months.	At month 24, the implant group improved better than the systemic therapy group in terms of letter gain (+6.0 vs +3.2, $p=0.16$) and vision-related quality of life improvement (11.4 vs 6.8 units, $p=0.043$). Only 12% of patients in the implant group had active uveitis ($p=0.001$). The two groups were comparable in terms of the proportion of patients with macular edema ($p=0.071$).
Kempen et al, ²⁴ 2017	Randomized controlled trials	215 patients with NIU were randomly assigned to receive systemic corticosteroids and immunosuppression or an intravitreal FA 0.59 mg implant and were followed up for 7 years.	Over 7 years, the mean BCVA improved from 61.7 to 55.8 in the implant group and from 65.0 to 66.2 in the systemic therapy group. There was an overall -10 dB loss in visual field sensitivity. The two groups were comparable in terms of uveitic activity ($p=0.69$) and macular edema ($p=0.30$). The implant group had more incidences of elevated intraocular pressure and glaucoma requiring treatment.
Pavesio & Heinz, ¹⁶ 2022	Prospective, randomized, double-blinded	59 patients with bilateral NIU of the posterior segment and two previous recurrences received an FA implant 0.2 μ g/day and were observed for 3 years.	The recurrence-free rate was higher in FA implant-treated eyes than fellow eyes (28.8% vs 5.1%, $p=0.001$). Over 3 years, BCVA improvement was greater in FA implant-treated eyes than fellow eyes (+9.6 vs -4.4 letters, $p<0.0001$). The FA implant group had rapid and consistent reduction in central foveal thickness and less frequent adjunctive intra/peri-ocular injection ($p<0.0001$) and topical corticosteroid use ($p=0.0041$).
Mahmud et al, ¹⁷ 2023	Retrospective	13 patients (19 eyes) with NIU received an FA implant and were followed up at months 2 and 6 month.	14 (74%) eyes achieved inflammatory control, with no additional therapy required, or had a 3-week tapered course of topical corticosteroids. Inflammatory control was inadequate in patients with CME.
Pockar et al, ¹⁸ 2023	Retrospective	9 patients (11 eyes) with chronic NIU and CME had an intravitreal FA implant 0.19 mg and were followed up for 52 weeks.	At 12 months, the mean CRT improved from 435.3 μ m to 296.5 μ m ($p=0.01$) and VA improved from logMAR 0.48 to 0.45 ($p=0.59$); only one eye gained >15 letters.
Hikal et al, ¹⁹ 2021	Retrospective	26 patients (34 eyes) with NIU and macular edema received an FA implant 0.19 mg and were followed up for 18 months.	70.6% of eyes had a completely dry macula, and 17.6% of eyes had decreased macular edema. 14.7% of eyes had relapsed macular edema requiring reinjection. VA improved in 12 eyes by 2 ± 1.2 lines; nine eyes had stable VA and five eyes had deteriorating VA.
Studsgaard et al, ²⁰ 2022	Retrospective	20 patients with chronic NIU associated with CME were treated with an FA implant 0.19 mg and were followed up for 2 years.	The mean BCVA improved at months 6, 12, and 18. CRT decreased by 45 μ m at month 12 ($p=0.006$). Four patients had relapsed NIU within 18 months and were treated with corticosteroids.
Triamcinolone acetonide			
Thorne et al, ²⁶ 2019	Randomized clinical trial	192 patients with uveitic macular edema were randomly assigned to receive periocular or intravitreal 40 mg triamcinolone acetonide implant or intravitreal 0.7 mg dexamethasone implant and were followed up for over 24 weeks.	All groups showed significant central subfield thickness reduction at week 8. At week 24, the two intravitreal groups were superior to the periocular group ($p<0.0001$) in terms of BCVA gain and proportion of eyes with resolved CME.

Abbreviations: BCVA=best-corrected visual acuity; CME=cystoid macular edema; CRT=central retinal thickness; FA=fluocinolone acetamide; NIU=non-infectious uveitis; VA=visual acuity

occlusion-related macular edema since 2009. Its action can last for up to 6 months. Since 2014, Ozurdex has been widely used to treat diabetic macular edema, particularly in pseudophakic patients who did not respond well to anti-vascular endothelial growth factor.⁹

In the LOUVRE2 study, Ozurdex was injected in 245 French patients with posterior segment inflammation secondary to NIU.¹⁰ Two months after treatment, 20.5% of patients had gained ≥ 15 letters (the mean was 6.2 letters for all patients). 18 months after treatment, 25.0% of patients had gained ≥ 15 letters in best-corrected visual acuity (BCVA). Additionally, the mean central retinal thickness (CRT) reduced by 27.4%, 18.5%, and 16.4% at months 2, 6, and 18, respectively. The mean vitreous haze score reduced significantly by 0.19 and 0.18 at months 2 and 6, respectively. The mean quality-of-life score significantly increased 2 months after the injection. 50.0% of patients were not indicated to receive an alternative or repeat treatment at month 6 because inflammation had sufficiently subsided and was deemed stabilized or improved. Yet, ocular hypertension, cataract progression, and conjunctival hemorrhage occurred as treatment-related adverse effects.

Similarly, a study of Turkish patients with NIU (predominantly idiopathic posterior uveitis) also found Ozurdex effective.¹¹ Six months after treatment, BCVA had improved from 0.55 to 0.35 logMAR ($p < 0.001$) and central foveal thickness had decreased from 386 to 302 μm ($p < 0.001$). The decrease in vitreous haze persisted for 6 months. 35% of the patients required a second Ozurdex injection after a median interval of 4.5 months. Patients with chronic CME had limited responses to the first injection because of their long-term intraocular inflammation.

A study of Canadian patients with UME showed significant reductions in CRT ($p < 0.001$) and improvements in BCVA ($p = 0.002$) 3 months after treatment with Ozurdex.¹² Second implants were administered if the CRT increased $> 10\%$ and $> 50 \mu\text{m}$; the median time to relapse was 6 months.

Ozurdex was reported to be safe and effective in a Chinese population with NIU (mainly idiopathic panuveitis).¹³ After 1 week and 1, 3, and 6 months of treatment, BCVA improved by 0.245, 0.437, 0.380, and 0.316 logMAR, respectively ($p < 0.001$), and CRT decreased from 649.1 μm at baseline to 340.9, 287.9, 357.2, and 387.0 μm , respectively ($p < 0.05$). However, 14.29% of eyes required additional topical therapy for a transient rise in IOP ($> 21 \text{ mmHg}$).

However, Ozurdex was reported to have a limited and short-lived effect on BCVA in 31 patients with UME mainly caused by idiopathic panuveitis.¹⁴ Three months after treatment, BCVA remained unchanged in 60% of patients and had deteriorated (a mean of 0.37 logMAR, $p < 0.01$) in 40% of patients. Six months after treatment, BCVA had deteriorated (a mean of 0.39 logMAR) in 56.5% of the eyes. At 3 months, 31.3% of eyes had a macular edema relapse. The mean CRT increased from 308 μm at 1 month to 340 μm

at 3 months to 442 μm at 6 months (3 vs 6 months, $p < 0.001$). Reimplantation was performed based on the visual acuity reduction and/or CRT increase. 83.3% of patients relapsed within 12 months of reimplantation; the mean time to relapse was 5.0 months. Relapsed patients required a new intravitreal implant or systemic immunosuppressants. There were no significant differences in BCVA ($p = 0.152$) and CRT ($p = 0.427$) after reimplantation or after first implantation. The high relapse rate and worsening BCVA do not support the use of Ozurdex to treat uveitis. These findings may be due to recruitment bias; patients with advanced uveitis and CME resistant to other treatment regimens were recruited. In patients with chronic macular edema, the photoreceptors may be permanently damaged, so the potential for improving their visual acuity is limited.

Fluocinolone acetonide

Fluocinolone acetonide is a selective glucocorticoid receptor agonist with high lipophilicity and potency. It is 5 times stronger than triamcinolone acetonide in anti-inflammation. Two fluocinolone acetonide intravitreal implants: RETISERT 0.59 mg (Bausch & Lomb, Rochester [NY], USA) and YUTIQ 0.18 mg (EyePoint Pharmaceuticals, Watertown [MA], USA) have been approved by the United States Food and Drug Administration to treat NIU, whereas a third, ILUVIEN 0.19 mg (Alimera Sciences, Alpharetta [GA], USA), has been approved to treat diabetic macular edema only.¹⁵ All three implants are designed to slowly release fluocinolone acetonide over 30 to 36 months. YUTIQ is injected with a 25-gauge needle, whereas RETISERT requires scleral fixation of the implant by a vitreoretinal surgeon. Various studies, notably the multicenter uveitis steroid treatment (MUST) trial, have illustrated the effect of intravitreal fluocinolone acetonide implants on improving BCVA, reducing CRT, and drying macular edema.¹⁶⁻²⁰

In the MUST trial, 117 patients with UME (intermediate, posterior, or panuveitis) were randomly assigned to either RETISERT 0.59 mg or systemic immunosuppression.²¹ Re-implantation was performed for patients with initial failure to control inflammation, systemic disorders requiring systemic therapy, or treatment-limiting toxicity. After 2 years of treatment, 71% of the eyes with RETISERT had improved UME ($\geq 20\%$ reduction in or normalization of macular thickness) and 60% had resolved edema (decrease in macular thickness to $< 240 \mu\text{m}$). The mean macular thickness reduced by 180 μm in the RETISERT group and by 109 μm in the systemic immunosuppression group ($p = 0.04$). The mean BCVA improved by +10 letters in both groups, with resolved and improved UME. Eyes with leakage on fluorescein angiography had 20% more improvement in UME compared with those without leakage ($p = 0.03$), but the two groups were comparable in terms of resolution of UME ($p = 0.49$). Baseline macular leakage was associated with better visual acuity (by 7 letters) 2 years after treatment. After 2 years of treatment, the two groups were comparable in terms of BCVA improvement ($p = 0.16$) and EuroQol-EQ5D health utility ($p = 0.060$).²² Compared

with systemic immunosuppression, RETISERT resulted in higher improvement in vision-related quality of life (+11.4 vs +6.8 units, $p=0.043$) and lower percentage of active uveitis (12% vs 29%, $p=0.001$), and lower (but not significantly) percentage of macular edema (22% vs 30%, $p=0.071$).²² However, eyes with RETISERT had higher risks of cataract surgery (80%, hazard ratio [HR]=3.3, $p<0.0001$), raised IOP requiring treatment (61%, HR=4.2, $p<0.0001$), and glaucoma progression (17%, HR=4.2, $p=0.0008$).²²

The MUST follow-up study evaluated the 7-year outcomes of RETISERT for UME.²³ Macular edema resolved in 94% of eyes after a median treatment time of 1.09 years. However, 43% of the eyes with macular edema relapsed by year 7; the relapse was associated with a thicker central macular thickness (HR=2.02, $p=0.007$) and being Black (HR=1.80, $p=0.039$). The presence of an epiretinal membrane was associated with lower probability of macular edema resolution (HR=0.74, $p=0.05$). Eyes with macular edema resolution gained a mean of 6.24 letters, whereas eyes with macular edema lost a mean of 8.65 letters ($p<0.001$). RETISERT could effectively control UME, but relapse was common.

In another MUST 7-year follow-up study, the mean BCVA decreased from 61.7 to 55.8 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the RETISERT group but improved from 65.0 to 66.2 letters in the systemic immunosuppression group.²⁴ There were no significant differences in uveitic activity ($p=0.69$) and macular edema ($p=0.30$) between groups. The RETISERT group had a higher incidence of elevated IOP necessitating treatment, whereas the systemic immunosuppression group had higher incidences of hyperlipidemia, hypertension, osteopenia, and fractures. Irreversible chorioretinal lesions were found in the RETISERT group, owing to multiple inflammatory recurrence. Hence, RETISERT may only control inflammation and CME in the short term, with risks of relapse in the long run, whereas systemic therapy may be more effective in improving BCVA.

Triamcinolone acetonide

Triamcinolone acetonide is a strong synthetic glucocorticoid with immunosuppressive and anti-inflammatory effects. It is commonly used to treat various ocular conditions, such as branch or central retinal vein occlusion, diabetic macular edema, and pseudophakic CME. It reduces vessel proliferation in choroid neovascularization, neovascular glaucoma, or proliferative ischemic retinopathies.²⁵ It is available commercially as Kenalog (40 mg/mL, Bristol-Myers Squibb, Princeton [NJ], USA) but is not yet licensed for periocular or intraocular injection; its effects last for at least 3 months. It is also available commercially as a preservative-free injectable suspension for uveitis known as Triesence (40 mg/mL, Alcon Laboratories, Geneva, Switzerland); its effects last for 3 months. Triesence has a lower risk of pseudo-endophthalmitis than Kenalog.

In the POINT randomized controlled trial, 192 patients with

UME (mainly intermediate or panuveitis) were randomly assigned to receive periocular triamcinolone acetonide 40 mg/mL injection (Kenalog), intravitreal triamcinolone acetonide 40 mg/mL injection (Triesence), or intravitreal dexamethasone 0.7 mg implant (Ozurdex).²⁶ All three groups showed significant central subfield thickness (CST) reduction at weeks 4, 8, 12, and 24 ($p<0.0001$). Triesence and Ozurdex were superior to Kenalog in resolving macular edema at week 4 ($p<0.0001$). Ozurdex was non-inferior to Triesence at week 8. At week 24, both Triesence and Ozurdex demonstrated significantly higher BCVA gains (+4 to +7 letters) and a higher proportion of eyes with resolved macular edema than Kenalog. Triesence and Ozurdex achieved similar BCVA at any time point. Complications reported were elevated IOP requiring anterior chamber paracentesis, vitreous hemorrhage, and hypotony. Both Triesence and Ozurdex were effective for the treatment of UME, but Ozurdex quickly became less effective over time and warrants earlier retreatment.

Suprachoroidal injection

The suprachoroidal injection route refers to administering drugs into the space between the sclera and choroid, targeting the choroid, retinal pigmental epithelium, and retina. The advantages of this route over the intravitreal route are that a higher drug concentration can be delivered to the posterior segment, and a lower drug concentration to the anterior segment and lens.²⁷ This reduces the risk of steroid-induced cataracts or glaucoma progression. Suprachoroidal injection is contraindicated in patients with active ocular or periocular infection. During the injection, the beveled end of the proprietary needle at 1 mm should avoid covering the outer sheath to reduce the risk of drug leaking out. In a porcine model, suprachoroidal injectable suspension of triamcinolone acetonide (CLS-TA) reduced ocular inflammation and vitreous cellular infiltration more effectively than intravitreal administration.²⁸ Commercially, Xipere (40 mg/mL, Clearside Biomedical, Alpharetta [GA], USA) is a CLS-TA available for the treatment of UME; it requires repeat injections every 12 weeks.

Studies have evaluated the effectiveness of CLS-TA in patients with uveitis (**Table 2**). In the AZALEA prospective trial, 37 patients with NIU (mainly chronic and idiopathic intermediate uveitis, with or without macular edema) were treated with two CLS-TA 4 mg via a proprietary microinjector at day 0 and week 12.²⁹ The mean BCVA improved from 68.9 at baseline to 75.0 at week 8 and 75.9 at week 24. The mean CST decreased by 15% from 335.9 μm at baseline to 284.0 μm at week 24. The proportion of patients with no vitreous haze improved from 44.7% at baseline to 89.5% at week 24. Four patients developed cataracts but did not require surgery. Six patients had elevated IOP from a mean of 13.3 mmHg at baseline to 15.2 mmHg at week 24. Four patients required an additional IOP-lowering eye drop, while three patients required two additional medications. Suprachoroidal CLS-TA was safe and effective in improving BCVA and macular edema.

Table 2. Studies of suprachoroidal steroid injection for non-infectious uveitis

Study	Study type	Patient characteristics	Main results
Henry et al, ²⁹ 2022	Prospective	37 patients with NIU with or without CME received two CLS-TA 4 mg 12 weeks apart and were followed up for 24 weeks.	At week 24, the mean BCVA improved from 68.9 at baseline to 75.9, and the mean CST improved from 335.9 to 284.0 μ m (a 15% decrease). The proportion of patients with a vitreous haze grade of 0 improved from 44.7% to 89.5%.
Khurana et al, ³³ 2022	Non-interventional extension study	28 patients with NIU-associated macular edema received two CLS-TA at baseline and week 12 and were followed up for 48 weeks and compared with five controls.	Over 48 weeks, the median rescue time was more in the treatment than control group (257.0 vs 55.5 days, $p<0.001$). The treatment group gained a mean of 12.1 letters by week 48 ($p=0.004$) and had CST reduction from 292.5 to 174.5 μ m ($p=0.001$).
Singer et al, ³² 2022	Post-hoc analysis	129 patients with NIU complicated by CME received two CLS-TA 4 mg 12 weeks apart and were compared with sham-controls.	At week 24, outcomes were better in the treatment than control group in terms of letter gain (15.7 vs 10.9 letters) and CST reduction (174.0 vs 148.5 μ m, $p=0.040$).
Merrill et al, ³¹ 2023	Post-hoc analysis	117 uveitic macular edema patients received CLS-TA with or without systemic corticosteroids or steroid-sparing therapy and were followed up for 24 weeks.	In patients without steroid-sparing therapy, outcome was better in the CLS-TA than control group in terms of the mean BCVA gain (15.6 vs 4.9 letters, $p<0.001$) and mean CST reduction (169.8 vs 10.3 μ m). In patients with steroid-sparing therapy, the two groups were comparable in BCVA and CST.
Yeh et al, ³⁰ 2020	Masked, randomized trial	160 patients with CME secondary to NIU were randomly assigned to receive CLS-TA or sham injection at weeks 0 and 12 and were monitored for 24 weeks.	Outcome was better in the CLS-TA than control group in terms of the proportion of patients with improvement of ≥ 15 ETDRS letters (46.9% vs 15.6%, $p<0.001$) and CST reduction (153 vs 18 μ m, $p<0.001$).

Abbreviations: BCVA=best-corrected visual acuity; CLS-TA = injectable suspension of triamcinolone acetonide; CME=cystoid macular edema; CST = central subfield thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; NIU=non-infectious uveitis

The PEACHTREE was a phase III randomized trial assessing the efficacy of suprachoroidal CLS-TA in patients with CME secondary to NIU.³⁰ A total of 160 patients (most with intermediate uveitis and panuveitis) were randomly assigned in a 3:2 ratio to receive CLS-TA 4 mg or sham injection at day 0 and week 12. Patients were allowed systemic corticosteroids, including oral prednisolone ≤ 20 mg/day. The patients had intraretinal or subretinal fluid with a CST ≥ 300 μ m. At week 24, more patients in the CLS-TA group than in the placebo group achieved an improvement of ≥ 15 ETDRS letters (46.9% vs 15.6%, $p<0.001$). Early BCVA improvement at week 8 was observed in the CLS-TA group, with more proportion of patients attaining >70 ETDRS letters (49% vs 15%, $p<0.001$). At week 24, the CLS-TA group had greater reduction in CST (153 vs 18 μ m, $p<0.001$). At week 4, more patients in the CLS-TA group achieved CME resolution (53% vs 2%, $p<0.001$). A smaller proportion of patients in the CLS-TA group required rescue therapy (13.5% vs 72%, $p<0.001$).

A post-hoc analysis of the PEACHTREE study demonstrated the benefits of CLS-TA in patients with UME who received sham controls or suprachoroidal CLS-TA with or without systemic corticosteroids and/or steroid-sparing therapy.³¹ At week 24, among those without systemic corticosteroids and steroid-sparing therapy, the CLS-TA group achieved better outcome than controls in terms of BCVA gain (15.6 vs 4.9 letters, $p<0.001$) and CST reduction (169.8 vs 10.3 μ m, 95% confidence interval [CI] for difference= -219.1 to -99.9 μ m, $p<0.001$). Likewise, among those with systemic corticosteroids and/or steroid-sparing therapy, the CLS-TA group achieved better outcome than the systemic therapy

alone group in terms of BCVA improvement (+9.4 vs -3.2 letters, $p=0.019$) and CST reduction (-108.3 vs -43.5 μ m, 95% CI difference= -163.2 to 33.6 μ m, $p=0.190$), but the difference in CST reduction was not significant.

In another post-hoc analysis of the PEACHTREE study, patients were randomly assigned to receive CLS-TA with or without rescue therapy.³² The median time to the first rescue therapy (mainly topical or intravitreal corticosteroids) was 84 days. At week 24, the CLS-TA alone group had better BCVA gain (15.7 vs 10.9 letters, $p=0.080$) and CST reduction (174.0 μ m vs 148.5 μ m, $p=0.040$).

The MAGNOLIA extension study evaluated 33 patients with UME from the PEACHTREE trial who were followed up for 48 weeks without rescue therapy.³³ Most patients had chronic and idiopathic posterior uveitis of insidious onset. The median time to rescue therapy was longer in the CLS-TA group than in controls (257.0 vs 55.5 days, $p<0.001$). At week 48, the CLS-TA group had BCVA gain of 12.1 letters ($p=0.004$) and CST reduction from 292.5 μ m at baseline to 174.5 μ m ($p=0.001$). The percentage of patients with no vitreous haze increased from 25.0% at baseline to 85.7% at week 48. Regarding adverse events, seven patients developed cataracts and four developed elevated IOP. Overall, the clinical trials PEACHTREE, MAGNOLIA, and AZALEA support the use of suprachoroidal CLS-TA for patients with UME.

Suprachoroidal injection enables more targeted delivery of steroids to chorioretinal structures than intravitreal injection, while reducing drug exposure in the anterior segment.³⁴

Treatments via the suprachoroidal route effectively improve visual acuity, reduce CST, and resolve vitreous haze. Nonetheless, suprachoroidal injection was associated with the risk of vitreous detachment, which occurred in 5.2% of patients.³⁰ Additionally, suprachoroidal hemorrhage and retinal detachment can occur, although none did in the AZALEA study.

Periocular injections

Subtenon injection refers to drug administration into the potential space between the Tenon's capsule and sclera, usually at the superotemporal quadrant. After going through the conjunctiva and Tenon's capsule, a half-inch 27-gauge needle is then advanced posteriorly along the outside of the globe. This route is contraindicated in patients with previous extensive vitreoretinal surgery, strabismus surgery, or eye trauma. Orbital floor injection, a localized deposition of steroids into the orbital floor, can lead to cataract progression and increased IOP, although the risks are lower than those of intravitreal injection.³⁵ Subtenon triamcinolone acetonide injections, which last for 2 to 3 months, improve visual acuity and decrease central macular thickness (**Table 3**).

Pediatric patients with uveitis have a worse prognosis owing to sight-threatening complications such as secondary cataracts and glaucoma. In a retrospective review, 30 pediatric patients (48 eyes) with NIU (63% being pars planitis) received subtenon triamcinolone acetonide 20 mg injection with topical anesthesia.³⁶ At 3 months after treatment, inflammation had improved in 41 of the 48 eyes, with the number of vitreous cells reduced and macular edema/optic nerve edema resolved. Of 18 eyes with baseline central macular thickness of ≥ 300 μm or the presence of cystic intraretinal fluid, 14 (77.8%) had resolved in 3 months. Oral corticosteroids and systemic immunomodulatory therapy were tapered and eventually stopped in all patients. Visual acuity improved in both the right eyes ($p=0.0002$) and left eyes ($p=0.007$). However, 15% of the eyes developed cataracts after 1 year, and the percentage increased to 33.3% after 2 years. Moreover, 12.5% of the eyes developed ocular hypertension and required IOP-lowering medication.

A retrospective review analyzed 115 adults with NIU (mainly

idiopathic posterior or panuveitis) who received in a 1:2 ratio either modified posterior subtenon injection or trans-septal injection of triamcinolone acetonide 40 mg/mL.³⁷ At 6 months, the proportion of patients with visual acuity of 20/40 or better was higher in the posterior subtenon injection group than in the trans-septal injection group (72.2% vs 51.9%, $p=0.02$). In the former group, logMAR visual acuity improved from 0.35 at baseline to 0.22 at 6 months ($p=0.002$), and the mean central macular thickness decreased from 455 μm to 359 μm ($p=0.048$); 85.7% of patients had vitritis quiescence at 6 months. In another study,³⁸ seven patients had steroid-induced elevated IOP, and four required cataract surgery. This highlights the efficacy of subtenon delivery of triamcinolone acetonide in improving visual acuity and macular edema, despite its side effects of cataracts and glaucoma progression.

Intravenous administration of methylprednisolone

High-dose intravenous methylprednisolone pulse (IVMP) is widely used for systemic juvenile idiopathic arthritis, systemic lupus erythematosus, and optic neuritis (**Table 4**). Methylprednisolone is injected into the bloodstream so that the steroid can take effect within 6 to 8 hours. Delayed control of ocular inflammation correlates to poor visual outcomes.³⁹ IVMP rapidly suppress inflammation and the recurrence of immune-mediated disorders. It is used in severe cases of NIU with unfavorable visual prognostic factors including dense vitreous haze or macular edema.

In a retrospective study of 56 children with active idiopathic NIU who received high-dose IVMP of 10 to 30 mg/kg/day for 3 days and were followed up for a median of 2.7 years.⁴⁰ Of them, 30 had additional methotrexate and 13 had additional biologic disease-modifying anti-rheumatic drugs because of failure to develop a sustained response. Visual acuity improved from 0.52 ETDRS letters at baseline to 0.69 ETDRS letters at 3 months ($p<0.001$) to 0.78 ETDRS letters ($p<0.001$) at 6 months. Optic disc edema decreased from 30% to 13% ($p<0.001$) and macular edema from 15% to 4% ($p=0.01$). Compared with patients with one IVMP, patients with ≥ 3 IVMP had fewer relapse events and required fewer eye surgeries for intraocular complications or fewer biologic disease-modifying anti-rheumatic drugs. However, patients

Table 3. Studies of periocular steroid injection for non-infectious uveitis (NIU)

Study	Study type	Patient characteristics	Main results
Jung et al, ³⁸ 2022	Retrospective	30 pediatric patients with NIU received subtenon triamcinolone acetonide 20 mg injection with topical anesthesia and were followed up for 6 months.	The level of inflammation – defined by the number of vitreous cells or the presence of macular edema/optic nerve edema – improved in 41 out of 48 eyes. Of the 18 eyes with cystoid macular edema, 14 resolved in 3 months. Visual acuity improved in both right eyes ($p=0.0002$) and left eyes ($p=0.007$).
McKay et al, ³⁷ 2021	Retrospective	115 patients with NIU received modified posterior subtenon or trans-septal triamcinolone injection 40 mg/ mL and were followed up for 6 months.	At 6 months, the proportion of patients with visual acuity of 20/40 or better was higher in the posterior subtenon injection group than in the trans-septal injection group (72.2% vs 51.9%, $p=0.02$). In the former group, logMAR visual acuity improved from 0.35 to 0.22 ($p=0.002$), and the mean central macular thickness decreased from 455 μm to 359 μm ($p=0.048$); 85.7% of patients had vitritis quiescence at 6 months.

Table 4. Studies of systemic steroid for non-infectious uveitis

Study	Study type	Patient characteristics	Main results
Schnabel et al, ⁴⁰ 2020	Retrospective	56 patients with juvenile NIU received IVMP 10-30 mg/kg/day for 3 days. Most had additional biologic disease-modifying anti-rheumatic drugs.	At month 6, visual acuity improved from 0.52 to 0.78, and papillary edema ($p<0.001$) and macular edema ($p=0.01$) reduced significantly. Visual acuity of <0.3 were more likely to occur in patients with three to five IVMP than in patients with one IVMP (44% vs 11%, $p=0.023$).
Vegas-Revenge et al, ³⁹ 2022	Retrospective	112 patients with severe NIU refractory to oral corticosteroids or biologics received IVMP 80-1000 mg every 24 hours for 2-5 days and were followed up for 30 days.	At 1 month, the mean best-corrected visual acuity improved from 0.46 to 0.74 ($p<0.05$), and macular thickness reduced from 409.7 to 275 μm ($p<0.05$). The mean basal Tyndall for vitritis reduced from 0.87 to 0.08 ($p<0.05$); only 5% of patients had residual vitritis.
Namba et al, ⁴² 2022	Retrospective	157 patients with relapsed NIU secondary to Vogt-Koyanagi-Harada disease or sarcoidosis received systemic corticosteroids for 12 months.	The mean total steroid dose over 12 months for all patients was 3874 ± 2775 mg. A higher total steroid dose was associated with immunosuppressant use ($p=0.0196$). The mean treatment time was 318.7 ± 89.3 days. 39.5% of patients had a subsequent relapse.

Abbreviations: IVMP=intravenous methylprednisolone pulse; NIU=non-infectious uveitis

with visual acuity of <0.3 were more likely to receive more IVMP (44% had three to five IVMP vs 11% had one IVMP, $p=0.023$).

In a multicenter retrospective study of 112 NIU patients (68 of them had panuveitis that was idiopathic or secondary to Vogt-Koyanagi-Harada disease) who received IVMP 80 to 1000 mg every 24 hours for 2 to 5 days.³⁹ At 1 month, the mean BCVA improved from 0.46 to 0.74 ($p<0.05$), and macular thickness reduced from 409.7 μm to 275 μm ($p<0.05$). Of 50 patients with CME, 38 had resolution of macular edema. The mean basal vitreous haze score for vitritis reduced from 0.87 to 0.08 ($p<0.05$); only 5% of patients had residual vitritis; no patient had grade 3 or 4 vitritis. 69.3% of patients with retinitis and 69.9% of patients with choroiditis had significant BCVA improvement ($p<0.05$). Regarding adverse events, three patients had respiratory infections and one had uncontrolled hyperglycemia and oral candidiasis.

Long-term systemic corticosteroid use is associated with diabetes, hypertension, and glaucoma, so the maximum recommended dose is ≤ 7.5 mg/day.⁴¹ Accurate dosage of systemic corticosteroids prevents relapse. In a retrospective observational study of systemic steroids for relapsed NIU secondary to Vogt-Koyanagi-Harada disease or sarcoidosis, 157 patients with relapsed non-infectious intermediate or posterior or panuveitis received systemic corticosteroids (initial dose, 8.5 ± 7.1 mg/day) for 12 months.⁴² The mean total steroid dose for all patients was 3874.0 ± 2775.0 mg. The total dose was highest at 1 month and decreased every 3 months until 12 months. The mean duration of treatment was 318.7 days; the mean days of high dosage (≥ 10 mg/day) was 178.5. A higher total steroid dose was associated with immunosuppressant use ($p=0.0196$). 39.5% of patients had a subsequent relapse. Steroid-related adverse events included cataracts, worsening diabetes, femoral head necrosis, and central serous chorioretinopathy. Therefore, patients who receive high-dose corticosteroids for a long time require additional immunosuppressants to prevent NIU relapses.

Topical administration of dexamethasone-cyclodextrin nanoparticles

The topical steroid route refers to the administration of drugs into the ocular system via the cornea or conjunctival epithelium. It is mainly reserved for anterior uveitis because of its limited penetration to the cornea and sclera. Topical therapy reduces the risk of complications arising from intraocular injections such as retinal detachment, vitreous hemorrhage, and endophthalmitis.⁴³ Cyclodextrin, an oligosaccharide, promotes ocular drug delivery by dissolving the lipophilic drug molecule in the aqueous tear film.⁴⁴ The cyclodextrin is left in the tear film and flows into the nasolacrimal ducts. However, topical therapy for NIU is not yet approved for clinical use.

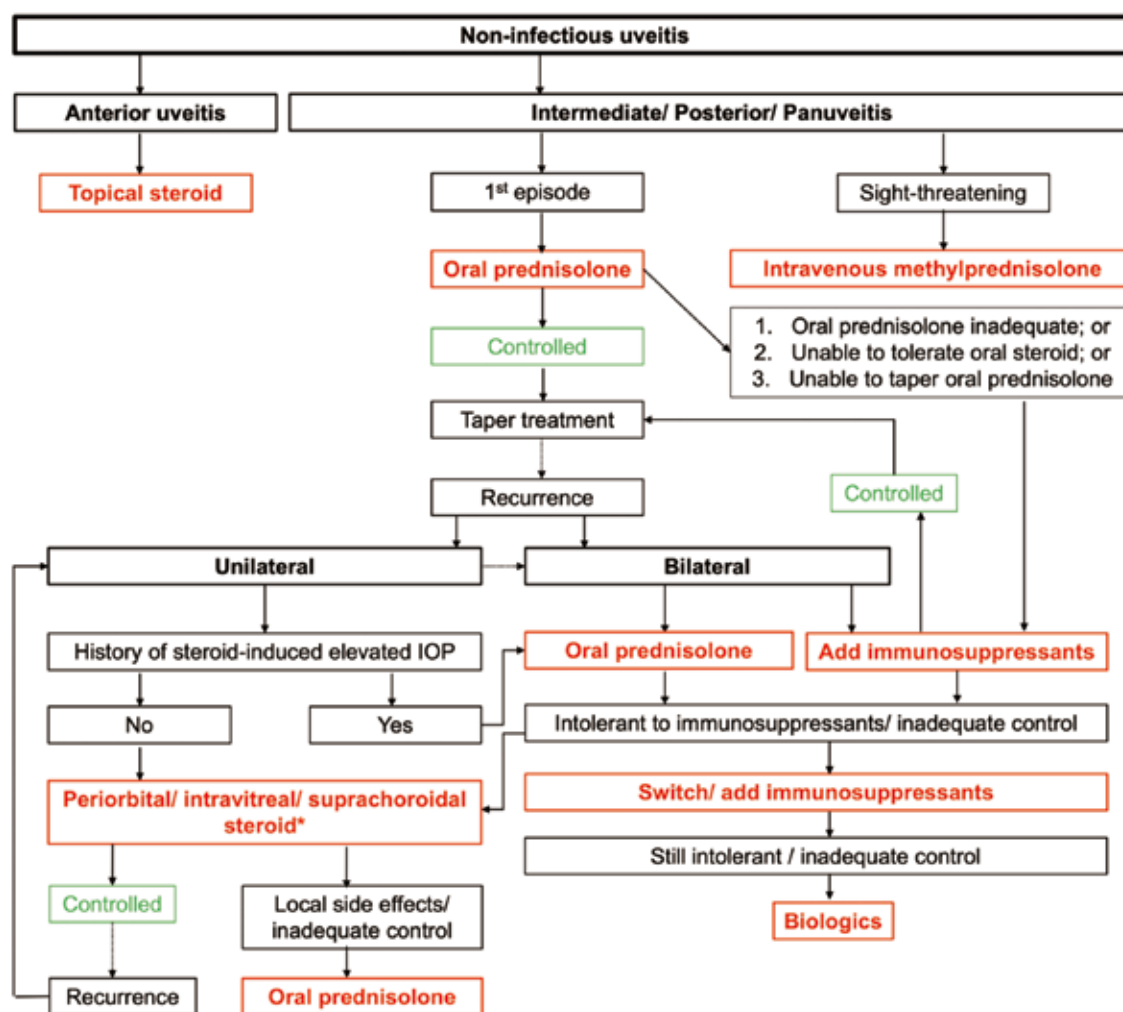
A study reported five patients (8 eyes) with idiopathic intermediate uveitis, macular edema, and vitritis received 1.5% dexamethasone-cyclodextrin nanoparticle drops four times a day for 4 weeks, followed by 4 weeks of tapering doses (Table 5).⁴⁵ The median BCVA improved from 0.2 logMAR at baseline to 0.15 logMAR at week 4 ($p=0.034$) but returned to 0.2 logMAR at week 12. Central macular thickness improved from 435 μm at baseline to 350 μm at week 12 ($p<0.05$). Four eyes had resolution of CME at week 8 and maintained at week 12. Of the three eyes with vitritis, two resolved at week 12. No adverse event was reported. Topical steroids have good penetration and minimal adverse effects, making it a promising non-invasive therapy for intermediate uveitis.

Clinical guidelines for steroid use in intermediate and posterior uveitis

Figure 2 illustrates the flowchart of treatment options for uveitis. Systemic or periocular steroids are the first-line treatment for non-infectious intermediate, posterior, or panuveitis. Subtenon or orbital floor injections of triamcinolone acetonide are recommended for unilateral uveitis with or without CME. Systemic steroids, oral prednisolone, and IVMP are recommended for bilateral

Table 5. Study of topical steroid for non-infectious uveitis (NIU)

Study	Study type	Patient characteristics	Main results
Shulman et al, ⁴⁵ 2015	Prospective	Five patients (eight eyes) with NIU with cystoid macular edema and/or vitritis received 1.5% dexamethasone-cyclodextrin nanoparticles drops 4 times a day for 4 weeks, followed by tapering to one drop every 10 days. Patients were monitored for 4 weeks without treatment and then further for 12 weeks.	At week 12, the median best-corrected visual acuity remained unchanged at 0.2 logMAR, and the central macular thickness improved from 435 to 350 μ m ($p<0.05$). All eyes showed complete resolution of cystoid macular edema at week 8. Two of the three eyes with vitritis resolved by week 12.



Route	Advantages
Intravitreal	Minimal systemic adverse effects Longer action than topical drops Can target the posterior segment Used in patients with vitritis or macular edema who are unlikely to respond or have failed to respond to periocular injection
Suprachoroidal	Minimal systemic adverse effects Targets posterior pathology without elevating intraocular pressure or causing cataracts
Periorbital	Minimal systemic adverse effects Longer action than topical drops Can reach the posterior segment

Figure 2. Flowchart of steroidal administration options for non-infectious intermediate, posterior, or panuveitis. Copyright: College of Ophthalmologists of Hong Kong.

and/or severe uveitis and those not responding to periocular steroid injections. Steroid-sparing agents (including methotrexate, mycophenolate mofetil, and azathioprine) are second-line treatments, whereas biologic disease-modifying anti-rheumatic drugs (such as adalimumab and infliximab) are third-line options. If medical therapy fails to control the vitreous haze, retinal detachment, or CME, vitrectomy should be considered, with laser therapy as an adjuvant treatment to peripheral retinal neovascularization.⁴⁶ There is no guideline on the use of suprachoroidal /intravitreal/ periocular steroid injections; route selection is based on clinician preference.

Management of NIU during the COVID-19 pandemic

Patients with COVID-19 are at risk of cytokine storm involving interleukin-6 and interleukin-10 and reactivation of uveitis. The World Health Organization recommended avoiding the use of systemic corticosteroids in patients with severe COVID-19.⁴⁷

In the COPE study, 91.5% of patients with NIU received systemic immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil) and 14.5% of patients with NIU received biologics.⁴⁸ In 18% of patients without COVID-19, the dosage of systemic immunosuppressants was reduced to decrease the risk of infection. Of 163 patients, 53 had a relapse. 25 of the 53 patients had dosage reduced by uveitis experts or stopped medication by self. Uveitis experts preferred oral over intravenous steroids and tapering dosage despite active inflammation. Immunosuppressants and/or biologics should not be used when COVID-19 is suspected or confirmed. Local corticosteroid therapy is preferred (over systemic therapy). Multidisciplinary care is essential to manage NIU during the COVID-19 pandemic; for example, rheumatologists can help monitor drug effectiveness and safety.⁴⁹

Retina microvasculature and perfusion can be adversely affected by COVID-19. Retinal hemorrhage, cotton wool spots, and drusen can occur in acute patients with COVID-19. The mean vein diameter is higher in infected patients, which positively correlates with disease severity.⁵⁰

In the long term, post-COVID patients can develop retinal vessel changes, namely, narrower arteries and veins on fundus examination.⁵¹ The macular and peripapillary retinal nerve fiber is thinner in patients who had recovered from COVID. This could be due to neurodegeneration of the retinal vascular system or central nervous system after infection. These irreversible changes can affect retinal tissue perfusion and function in the long run.

Conclusion

Corticosteroids including dexamethasone, fluocinolone acetonide, triamcinolone acetonide, and methylprednisolone are effective for the management of NIU. They can be administered via the intravitreal, suprachoroidal, periocular, and systemic routes and even via topical nanoparticles. Corticosteroids significantly improve visual acuity and macular edema and should be the first-line treatment for NIU.

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.

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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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Ulcerated conjunctival mass as an initial presentation of idiopathic orbital inflammatory disease: a case report

Ivan Hong Wan Lau^{1,2}, MBBS, AFCOphth (HK); Tracy Yuen Ting Kwok^{2,3}, MBChB, FCOphth (HK); Hunter Kwok Lai Yuen^{2,3}, MBChB, FRCOphth, FRCS(Ed), FCOphth (HK), FHKAM (Ophthalmology), DipClinDerm (London)

¹Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong SAR, China

²Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China

³Department of Ophthalmology, Hong Kong Eye Hospital, Hong Kong SAR, China

Correspondence and reprint requests:

Dr Hunter Kwok Lai Yuen, Department of Ophthalmology, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong SAR, China.

Email: hunterklyuen@gmail.com

Abstract

A 62-year-old Chinese woman, with a history of immunoglobulin A nephropathy, presented with an ulcerative conjunctival lesion and anterior orbital inflammation. No infective foci were found, and her symptoms were not alleviated by antibiotic treatment or drainage of the lesion. She was diagnosed with idiopathic orbital inflammatory disease, also known as orbital pseudotumor, which completely resolved with oral corticosteroid treatment. To the best of our knowledge, this is the first documented case of idiopathic orbital inflammatory disease that initially presented with an ulcerative conjunctival lesion. We illustrate our stepwise diagnostic approach and management of the disease.

Key words: Administration and dosage; Conjunctival disease; Diagnostic imaging; Drug therapy; Glucocorticoids; Orbital pseudotumor

Introduction

Idiopathic orbital inflammatory disease (IOID), also known as nonspecific orbital inflammation or orbital pseudotumor,

is a benign, non-infectious, inflammatory condition of the orbit.¹ Its clinical presentation varies but generally includes periocular erythema, proptosis, chemosis, pain, extraocular motility limitation, and visual disturbance.² IOID can be categorized based on the predominantly inflamed anatomical area into anterior, posterior, diffuse, lacrimal, and myositic.³ The anterior and diffuse subtypes are characterized by pain, eyelid swelling, ptosis, and occasionally distinct inflammation of the globe, presenting as uveitis, papillitis, optic neuropathy, and exudative retinal detachment. To the best of our knowledge, there has been no report of IOID that initially presented as ulcerative conjunctival lesions. Here, we present this atypical IOID case and illustrate our stepwise diagnostic approach and management of the disease.

Case presentation

In February 2022, a 62-year-old Chinese woman presented with a 5-day history of painful swelling of the left upper and lower lids and blurred vision. She denied any history of ocular or facial trauma, dental procedures, or sinusitis symptoms. Visual acuity of her left eye was finger-counting only. Intraocular pressure (IOP) was raised to 25 mmHg. There were diffuse swelling of the left upper and lower lids and copious discharge. There were a 4-mm proptosis and limitation of extraocular motility in all directions. A firm ulcerative conjunctival mass in the inferior bulbar and forniceal conjunctiva was noted (**Figure 1**). Her right eye



Figure 1. A firm ulcerative lesion located in the inferior bulbar and forniceal conjunctiva of the left eye.

was unaffected, with visual acuity of 1.0, normal IOP, and no orbital inflammation.

Salient past medical history included immunoglobulin A (IgA) nephropathy, which had been confirmed by a renal biopsy and immunofluorescence 9 years before the current presentation when she developed hematuria and acute renal failure. She had been treated with systemic corticosteroids and immunosuppression for 3 years until she refused further medication because she had general malaise and fatigue that she perceived to be related to immunosuppression. No relapse occurred after she stopped treatment. The patient had recurrent skin ulcers on her neck, trunk, hands, limbs, and axillary region, requiring multiple excisions over the past decade. Histopathology of the lesions was ulceration or granulation tissue. She had no history of oral or genital ulcers, inflammatory joint pain, abdominal pain, abnormal bowel output, or skin rash/purpura.

She was admitted for computed tomography and was administered empirical intravenous ceftriaxone and metronidazole. She remained afebrile although there was mild leukocytosis and elevated anti-nuclear antibody at a titer of 1:160. Test results for anti-neutrophil cytoplasmic antibodies and immunoglobulin G4 were negative. Computed tomography of the orbits, brain, and paranasal sinuses revealed increased fat stranding in the left anterior orbit and a gaseous rim-enhancing collection, suggestive of left orbital cellulitis with anterior orbital abscess formation without retrobulbar extension (**Figure 2**).

The lesion was incised and drained through the left lower lid. However, the patient developed orbital compartment syndrome, which was not alleviated by topical or systemic pressure-lowering medications. A lateral canthotomy and cantholysis was performed to reduce the orbital pressure. The patient's ears, nose, and throat were examined, and no signs of sinusitis or underlying infective foci were found.

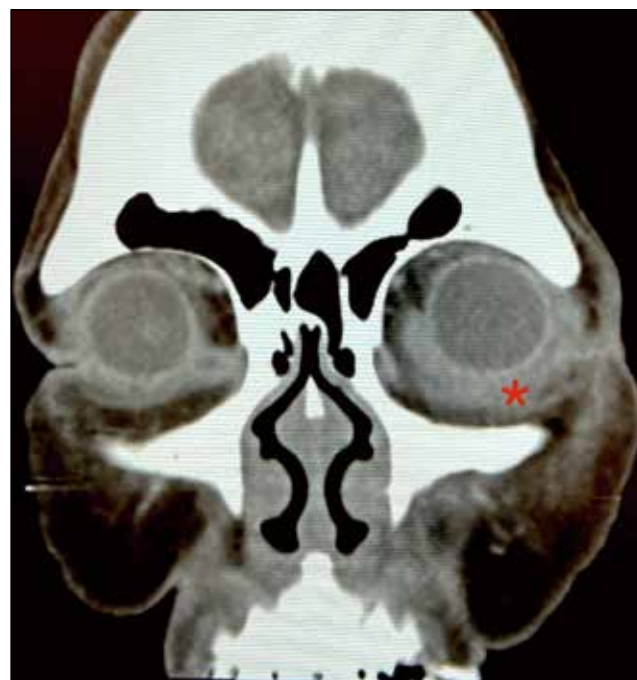


Figure 2. Computed tomography showing increased fat stranding of heterogeneous density in the left inferior orbit (asterisk), soft-tissue thickening in the left periorbital region, and clear paranasal sinuses.



Figure 3. At 2 months after oral steroid treatment, the left eye showing a marked reduction in orbital inflammation and complete resolution of the ulcerative conjunctival lesion.

The conjunctival mass was biopsied; histological analysis showed chronically inflamed tissue but no evidence of underlying infection. Given the patient's limited improvement despite empirical antibiotic treatment, a negative eye swab, the abscess having been drained, and the absence of other active infective foci, she was administered 0.5 mg/kg of oral prednisone. Her pain, swelling, vision, and ocular motility rapidly improved and the conjunctival lesion gradually resolved (**Figure 3**). The oral prednisolone

regimen was tapered off within a month. Her visual acuity returned to 0.5 in 1 month and to 0.7 in 3 months. Residual corneal punctate erosion and dry eye disease were treated with lubricating eye drops.

Discussion

IOID covers a broad spectrum of inflammatory disease and affects various locations of the orbit. Its variable nature poses a diagnostic and therapeutic challenge. IOID can be classified by the timing of presentation (acute, subacute, chronic), histopathology (classic, granulomatous, sclerotic, non-specific), or the main location (anterior orbit, posterior orbit, diffuse, lacrimal, and myositic).^{3,4} However, none of the classifications has described a conjunctival ulcerative lesion.

IOID mainly affects middle-aged women.⁵ The main symptom of anterior IOID is external inflammation. Patients often present with palpebral erythema accompanied by painful swelling, conjunctival hyperemia and chemosis, and limited ocular motility. Scleral involvement is possible.⁶ Although our patient's presenting symptoms and signs were consistent with the classic description of anterior IOID, the conjunctival ulcerative lesion was peculiar. Differential diagnoses of an ulcerated conjunctival mass include neoplastic, autoimmune, and infective pathologies. Ocular surface tumors may present as either melanotic or non-melanotic conjunctival mass, which can undergo ulcerative changes.⁷ Conjunctival ulcers are seen in autoimmune disorders (such as Behcet's disease⁸ and Crohn's disease⁹) and in infections (such as tuberculosis and herpes simplex).¹⁰ Although there are no prior reports of ulcerative conjunctival lesions in IOID or IgA nephropathy, autoimmune diseases (such as Crohn's disease, systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, and ankylosing spondylitis) are associated with IOID.¹ In fact, 10% to 84% of patients with IOID have a history of autoimmune or atopic disorders.¹ However, presentation of ulcerative conjunctival lesions as a sign of IOID in a patient with IgA nephropathy has never been reported.

IgA nephropathy is a common cause of glomerulonephritis.¹¹ It is characterized by clinically microscopic or macroscopic hematuria and, less commonly, acute renal failure and IgA antibody deposits in the glomeruli. Treatments with systemic corticosteroids or immunosuppressive agents have mixed results.¹¹ IgA vasculitis with nephritis involves IgA deposits in the glomeruli. It predominantly affects children and adolescents but can present at any age. It is characterized by purpuric rash over the lower extremities without thrombocytopenia or coagulopathy, with some lesions potentially becoming ulcerative.¹² Other clinical features include polyarthralgia, abdominal pain, and in 30% to 50% of patients, nephritis,¹¹ but presentation of conjunctival ulcerative lesions has never been described in either IgA nephropathy or IgA vasculitis with

nephritis.

Systemic corticosteroids are first-line treatment for IOID, with a 75% response rate.¹ IOID can be diagnosed by a response to corticosteroids, which negates the need for a surgical biopsy of inflamed orbital tissues.¹³ However, corticosteroids can alter cellularity and compromise diagnostic accuracy.¹ Furthermore, high-dose corticosteroids can deceptively improve both infective and inflammatory pathologies.¹⁴ In our patient, we effectively managed and ruled out infective etiologies before commencing a course of oral corticosteroids; the patient responded favorably with complete resolution of the orbital inflammation and conjunctival lesion.

Conclusion

We successfully treated with oral corticosteroids an atypical IOID that initially presented as an ulcerative conjunctival lesion and anterior orbital inflammation. We illustrate our stepwise diagnostic approach and management of the disease. Further histopathological studies may elucidate the pathological association between IOID and ulcerative conjunctival lesions.

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.

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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 patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all treatments and procedures and for publication.

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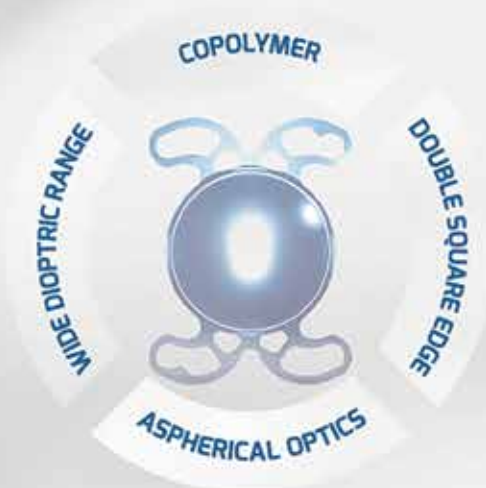


Stored at room temperature

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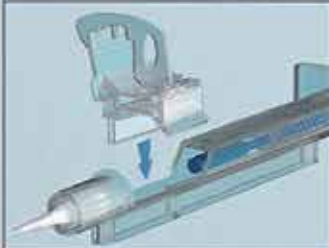
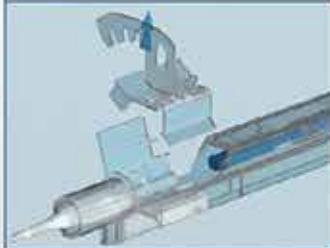
Aspherical IOL for mini-incision to reduce postoperative astigmatism and corneal aberrations



TECHNICAL SPECIFICATIONS

Material	Copolymer
Positioning	Bag
Total diameter	10.75 mm
Diameter of optical surface	6 mm
Vaulting	5°
Optics shape	Aspheric biconvex / Concave convex
Square edge	Double
Estimated A constant	118.6 (OD to +40D) 119.9 (-3D to -1D)
Estimated A.C.D.	5.32 mm (OD to +40D) 6.08 mm (-3D to -1D)
Dioptric range	-10D to +30D (-10D to +10D incr. 1D; +10D to +30D incr. 0.5D)
Size of incision	1.8 mm (wound assisted); ~2.2 mm (into the bag)
Refractive index	1.46 at 35°C UV absorber

INSTRUCTION FOR USE OF THE PRELOADED VERSION

- 1** Insert the cartridge, containing the IOL, into the injector.
 
- 2** Apply viscoelastic solution first through the front hole (until is filled) and then a little through the rear hole.
 
- 3** Remove the clip of safety block by lifting it using your index and thumb fingers.
 
- 4** Close the cartridge sides together until the "click-lock" mechanism engages. Push forward the plunger softly and ensure that the silicone cushion correctly enters into the cartridge loading chamber.
 



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References:

1. Bellucci R, Curatolo MC. A new extended depth of focus intraocular lens based on spherical aberration. J Refract Surg. 2017;33(6):389-94.

2. SIFI internal data.

Abbreviations:

EDOF: extended depth of focus. IOL: intraocular lens. WELL: Wavefront Engineering Leading Lens.

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References: 1. AcrySof® IQ Vivity® Extended Vision IOL Directions for Use. 2. Alcon Data on File, US Patent 9968440 B2, May 15, 2018. 3. Alcon Data on File, TDOC-0055575. 09 Apr 2019. 4. Alcon Data on File, TDOC-0055576. 23-Jul-2019. 5. Alcon Data on File, TDOC-0056718. 18-Jun-2019. 6. Ligabue E, et al. ACRYSOF IQ VIVITY: Natural vision at a range of distances provided by a novel optical technology. *Cataract & Refractive Surgery Today*. April 2020 // 7. Alcon Data on file. A02062-REP-043696, Optical Evaluations of Alcon Vivity®, Symphony®, Zeiss® AT LARA® AT LISA IOLs. Feb 2020. 8. Lawless M. *Insight news*. "An IOL to change the cataract surgery paradigm?" available at "<https://www.insightnews.com.au/an-iol-to-change-the-cataract-surgery11paradigm/>". Accessed Date 17.07.202



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