HONG KONG JOURNAL of OPHTHALMOLOGY

June 2023 Vol. 27 No. 1 ISSN 1027-8230 Online ISSN 2957-7098

香港眼科醫學院

香港眼科學刊

The Official Publication of
The College of Ophthalmologists of Hong Kong

香港醫學專科學院出版社
HONG KONG ACADEMY OF MEDICINE PRESS

FASTER.[1-4]
EASIER.[*,5,6]
BETTER.[1,2,7,8]

INTRODUCING

The ***NEW*** **ARGOS® Biometer with Image Guidance by Alcon®** is the smarter planning solution that keeps efficiency and accuracy flowing through your clinic.

*Compared to VERION™ Reference Unit.
†Trademarks are the property of their respective owners.

1. Tamaoki A, Kojima T, Hasegawa A, et al. Clinical evaluation of a new swept-source optical coherence biometer that uses individual refractive indices to measure axial length in cataract patients. *Ophthalmic Res.* 2019;19:1-13. **2.** Shammas HJ, Ortiz S, Shammas MC, Kim SH, Chong C. Biometry measurements using a new large-coherence-length swept-source optical coherence tomographer. *J Cataract Refract Surg.* 2016;42:50-61. **3.** Hussaindeen JR, Mariam EG, Arunachalam S, et al. Comparison of axial length using a new swept-source optical coherence tomography-based biometer. *PLOS ONE.* December 2018. **4.** ZEISS† IOLMaster† 700 510k Submission 2015. **5.** VERION™ Reference Unit User Manual 2019. **6.** ARGOS® Biometer User Manual 2019. **7.** Whang W, Yoo Y, Kang M, Joo C. Predictive accuracy of partial coherence interferometry and swept-source optical coherence tomography for intraocular lens power calculation. *Sci Rep.* 2018;8(1):13732. **8.** Shammas HJ. Accuracy of IOL power formulas with true axial length versus simulated axial length measurement in 318 eyes using an OCT biometer. 2019 ASCRS ASOA Annual Meeting. May 2019.

Alcon

HK-ARB-2100001 App. 202111

Vision Planner | Advancing CATARACT SURGERY

CONTENTS

香港眼科學刊

香港眼科醫學院

HONG KONG
JOURNAL OF
OPHTHALMOLOGY

The Official Publication of
the College of Ophthalmologists
of Hong Kong

June 2023

Volume 27 Number 1

ISSN 1027-8230

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@netvigator.com

Published by
HONG KONG ACADEMY OF MEDICINE PRESS

EDITORIAL BOARD

Information for Authors

Aims and Scope

- 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.

Journal Policies

- The HKJO adheres to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org) and the Core Practices of the Committee on Publication Ethics (COPE; https://publicationethics.org).
- Submitted manuscripts must be original works that have not been published elsewhere (in whole, in part, or as a preprint) and are not under consideration by another publication.
- To improve the quality and clarity of published articles, the Journal recommends the use of reporting guidelines in the preparation of manuscripts, such as those advocated by the EQUATOR Network (http://www.equator-network.org/), for example, CONSORT for randomized trials, or CARE for case reports.
- Any sponsor(s) of the research involved, along with grant number(s) should be provided.
- All authors must provide a statement reporting any conflicts of interest. Where none exist, please state 'The authors have no conflicts of interest to declare.' Authors may use the ICMJE Conflict of Interest form.
- For all research involving living humans (including studies involving human tissue, retrospective studies, and database studies), an appropriate research ethics committee must be consulted. A statement must be included in the manuscript that provides the name of the research ethics committee and approval number (or waiver).
- A statement on consent must also be included, indicating how patient(s)/guardian(s) provided informed consent (eg, written or verbal), or that the requirement for patient consent was waived by the review board.
- The authors shall make available the complete data on which the manuscript is based. A statement describing how the data can be accessed must be included in the manuscript. For clinical trials and other large datasets, the Journal recommends that data are deposited in a public repository and shared using a permanent identifier (such as a DOI).
- For details of the Journal policies on publication ethics, including authorship, plagiarism, and processes for handling appeals or complaints, please see the Journal website.

Submissions

- Manuscripts should be submitted through the HKJO online submission system at https://hkjo.hk/index.php/hkjo/about/submissions. Please register for an account with the system and upload files according to the instructions. All files must be submitted through the system.
- Please provide a blinded manuscript as a single file. Any identifying information (eg, references to past publications, name of an author's institution) should be masked or removed from the blinded manuscript.
- Manuscripts should be submitted in Word format (.doc or .docx).
- Manuscripts must be written in English (US spellings as per the Merriam-Webster Dictionary).
- In general, manuscripts should be prepared following the 'IMRaD' structure as recommended by the ICMJE (http://icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html).
- For each author, please provide the full name, professional qualifications, and affiliation (where the study was conducted).
- The full name, postal address, telephone and fax numbers, and email address of the corresponding author must be provided. The corresponding author, on behalf of the authors, is responsible for all contact with the Journal.
- A structured abstract of ≤250 words is required for Review Articles and Original Articles. The abstract should provide a complete summary of the article, including the aims/purpose, main methods, key results, and conclusions. Abbreviations and clinical or technical jargon should be avoided.
- Tables should be typed using the 'Insert Table' feature of MS Word, with one item of data per cell and minimal formatting. Large tables may be provided in MS Excel format. Tables should be numbered and concisely titled. Abbreviations should be defined in footnotes.
- The number of figures should be restricted to the minimum necessary to support the textual material. Figures should be .JPG format with a resolution of ≥350 dpi and should be included in the manuscript file; large image files may be submitted separately. Legends should be provided for each figure to indicate the anatomical area and pathological condition shown. All symbols and abbreviations should be defined in the legend.
- The references should be numbered in the order in which they are first cited in the text. Each reference citation should be in superscript Arabic numerals after full-stops and commas. At the end of the article, the full list of references should be presented in Vancouver style. Include the names of all authors, title of the article, abbreviated name of journal, year of publication, volume number, and inclusive pages, in that order.
- Please refer to the latest ICMJE recommendations on Manuscript Preparation for further information on references and for general guidance on style: http://icmje.org/recommendations/browse/manuscript-preparation/

Peer Review

- HKJO operates a double-blind peer-review process. Details of the peer review process can be found on the Journal website.

Copyright

- On acceptance of an article for publication in HKJO, copyright of the article is transferred to the Journal.
- The Journal has a fully Open Access policy and publishes all articles under a Creative Commons license (CC BY-NC-ND 4.0). For any use other than that permitted by this license, written permission must be obtained from the Journal.

Correspondence

- All correspondence on editorial issues should be addressed to the Editorial Office (editorial@hkjo.hk).

香 港 眼 科 醫 學 院

THE HONG KONG JOURNAL OF OPHTHALMOLOGY
BEST ORIGINAL ARTICLE AWARD

Purpose

To encourage submissions to the *Hong Kong Journal of Ophthalmology* (HKJO) by trainees and fellows of the College of Ophthalmologists of Hong Kong (COHK).

Awards and Prizes

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

Eligibility

- One award is open to all fellows and members of the College; another one is limited to trainees only.
- Applicants must be a paid-up member or fellow of COHK at the time of submission.
- Trainees refer to those who have not been conferred the title 'FCOphthHK' at the time of submission.
- Only the first author of the article will be eligible for the prize. If the first author is not eligible for the award, i.e. not a member or fellow of COHK, then the order of consideration of awardee will be from the second author onwards to the last author.
- Original articles (including, but not limited to, prospective or retrospective clinical studies, observational studies, epidemiological studies, basic science studies, meta-analysis, etc) published in the HKJO during the year will automatically enter the selection process.
- Case reports (with case number <3), review articles and letters to the editor will not be eligible for this award.
- Submissions pending acceptance will not be eligible for the award.
- Entries will be based on the article as a unit, but not the author. Because of this, it is possible that one single author wins both awards, given that he/she is the first author of the two best original articles published that year (but he/she has to be a trainee in this case as one award is open for trainees only).

Selection Panel

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

Selection Criteria

- Originality
- Scientific merit
- Methodology
- Presentation style

Award Presentation Ceremony

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

A new chapter for the *Hong Kong Journal of Ophthalmology*

I am truly humbled to have been entrusted with the role of Editor-in-Chief of the *Hong Kong Journal of Ophthalmology* (HKJO) since June 2023. It is my great honor to work with our excellent editorial team and the College of Ophthalmologists of Hong Kong to advance the development of our Journal. My deep gratitude extends to my distinguished predecessors whose invaluable contributions elevated HKJO to its current renown. In particular, Dr Ian Wong and his editorial team (2015-2019) launched an online platform that made HKJO accessible and retrievable through Google Scholar. Subsequently, Dr Alvin Kwok and his editorial team (2019-2023) paved the way for indexing by (1) updating the Journal's online submission platform to meet the requirement of PubMed Central, (2) revising the author guidelines and submission processes to meet the standards of the International Committee of Medical Journal Editors, (3) reformatting the Journal according to the standards of the Directory of Open Access Journals (DOAJ), and (4) initiating continuous online publication.

With the mission to promote ophthalmology research in Hong Kong, we are fully committed to advancing the Journal's scientific standard and reputation. Getting HKJO indexed is thus crucial. Building on the solid foundation laid by Dr Wong and Dr Kwok and their teams, we are optimistic about getting HKJO indexed in the DOAJ soon. Afterwards, we shall prepare for indexing in PubMed Central.

Finally, I would like to acknowledge our dedicated Editorial Board. In particular, I am grateful to Dr Alvin Au who will continue to serve as Associate Editor. With the support of our ophthalmology community, we are fully committed to taking HKJO to new heights.

Jason CS Yam, MBBS (HK), MPH (HK), FRCSEd, FCOphth (HK), FHKAM (Ophth)
Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China

Correspondence and reprint requests:
Dr Jason CS Yam, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China.
Email: yamcheuksing@cuhk.edu.hk

ORIGINAL ARTICLE

AcuFocus IC-8 intraocular lens for myopic patients with cataract: a retrospective study

Alexander C Poon, MBBS FRACS FRANZCO; Myra B McGuinness, PhD MBiostat
Royal Victorian Eye and Ear Hospital, Melbourne, Australia

Correspondence and reprint requests:
Dr Alexander Poon, 184 High St, Doncaster 3108, Victoria, Australia. Email: alexpoon@ozemail.com.au

Abstract

Purpose: To retrospectively review visual outcomes of patients with myopia who were implanted with the IC-8 intraocular lens in the nondominant eye and a monofocal intraocular lens in the dominant eye at a private ophthalmology clinic in Australia.

Methods: We retrospectively reviewed medical records of consecutive patients aged ≥18 years who had myopia (≥-0.25 diopter) in both eyes and astigmatism (≤-2.50 diopters) in the nondominant eye and underwent bilateral cataract surgery and implantation of the IC-8 intraocular lens in the nondominant eye and a monofocal intraocular lens in the dominant eye between January 2018 and February 2020 at a private ophthalmology clinic in Australia. At 6 months, uncorrected monocular and binocular distance, intermediate, and near visual acuity was assessed. Dysphotopsia symptoms was evaluated with the Quality of Vision questionnaire.

Results: Medical records of 15 men and 10 women aged 28 to 79 (mean, 60.8±11.5) years of Chinese (n=16), Caucasians (n=8), and South Asian (n=1) ethnicity were reviewed. The mean spherical equivalent improved from -2.92 to -1.20 diopters in nondominant eyes and from -2.42 to -0.13 diopters in dominant eyes. Binocularly, 92%, 64%, and 100% of patients achieved uncorrected distance, intermediate, and near visual acuity of logMAR 0 or better, logMAR 0 or better, and logMAR 0.20 (N5) or better, respectively. The mean Quality of Vision questionnaire score was 32.1 for frequency, 25.4 for severity, and 23.9 for bothersomeness of dysphotopsia symptoms. The rate of laser capsulotomy was higher in eyes with the IC-8 intraocular lens than eyes with the monofocal intraocular lens (72% vs 48%, p=0.08).

Conclusions: The IC-8 intraocular lens can extend the depth of focus and is a good option for patients with myopia. It provides good binocular uncorrected distance, intermediate, and near visual acuity when used in conjunction with a monofocal intraocular lens in the dominant eye. Some patients may have dysphotopsia symptoms, but the symptoms are not frequent, severe, or bothering.

Key words: Cataract; Lens implantation, intraocular; Myopia; Visual acuity

Introduction

Modern cataract surgery and intraocular lens (IOL) implantation require consideration and correction of visual outcomes such as spherical errors and astigmatism. In patients with plano postoperative refractive target, over 90% achieved 0.30 logMAR (Snellen chart, 20/40) unaided and over 75% achieved 0.18 logMAR (Snellen chart, 20/30) unaided.[1,2] Optimizing the depth of focus is important so that patients are less reliant on optical correction for far, intermediate, and near distances.

The IC-8 IOL (AcuFocus, Irvine [CA], USA) is an aspheric hydrophobic acrylic monofocal IOL (6 mm in diameter) with an embedded opaque mini-ring (**Figure 1**). The central black opaque ring (3.23 mm in outer diameter) comprises polyvinylidene difluoride and carbon nano-particles. The small aperture in the center (1.36 mm in diameter) extends the depth of focus. Extending the depth of focus was first

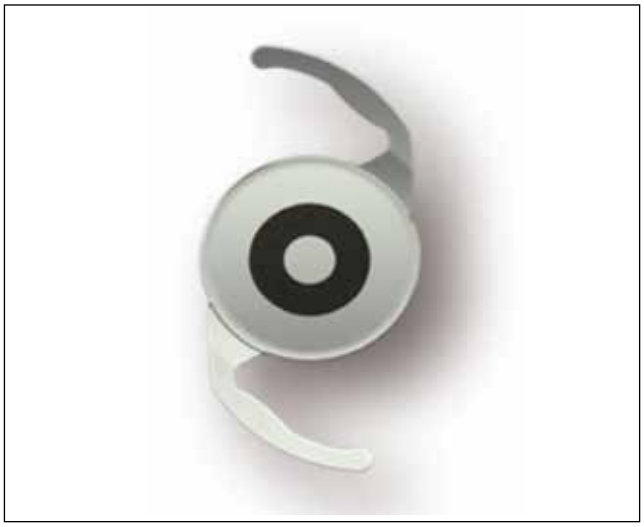


Figure 1. IC-8 intraocular lens with an opaque ring.

used in presbyopia correction using the Kamra corneal inlay. In 32 patients with emmetropia implanted with the Kamra corneal inlay, 74% achieved uncorrected near visual acuity (UNVA) of J3 and 87% achieved uncorrected intermediate visual acuity (UIVA) of 20/32 acuity at 5 years, but the uncorrected distance visual acuity (UDVA) decreased from a mean of -0.20 logMAR (Snellen chart, 20/12.5) to -0.10 logMAR (Snellen chart, 20/16).[3]

In 105 patients implanted contralaterally with a monofocal IOL (targeted for plano) and an IC-8 IOL (targeted for -0.75 diopter [D]), 99%, 95%, and 79% achieved 0.20 logMAR for binocular UDVA, UIVA, and UNVA, respectively.[4] In 109 patients implanted with the IC-8 IOL (targeted for -0.75 D), 90% achieved 0.30 logMAR or better unaided vision for far, intermediate, and near distances.[5] Patients with previous corneal refractive surgery or irregular astigmatism have also been reported to achieve good visual outcomes with the IC-8 IOL.[6-8]

Patients with low to moderate myopia for cataract surgery are often most difficult to please in terms of refractive outcome and unaided near vision, because they have excellent unaided near vision for most of their adult life until they developed cataracts. Monovision enables patients to see both far and near distances. The dominant eye is usually targeted for plano correction for far distance vision, whereas the nondominant eye is targeted for -0.50 D to -2.00 D to allow for intermediate and near vision. However, some patients cannot tolerate the loss of stereopsis owing to a lack of binocularity at any focal point as well as the distance blur on the nondominant eye. Using the IC-8 IOL in the nondominant near-targeted eye may potentially provide distance binocularity and a continuous range of near vision, compared with a typical monofocal IOL. We retrospectively reviewed visual outcomes of patients with myopia who were implanted with the IC-8 IOL in the nondominant eye and a monofocal IOL in the dominant eye at a private ophthalmology clinic in Australia.

Methods

We retrospectively reviewed medical records of consecutive patients aged ≥18 years who had myopia (≥-0.25 D) in both eyes and astigmatism (≤-2.50 D) in the nondominant eye and underwent bilateral cataract surgery and implantation of the IC-8 IOL in the nondominant eye and a monofocal IOL in the dominant eye between January 2018 and February 2020 at a private ophthalmology clinic in Australia. Patients with previous cataract surgery and implantation of monofocal IOL targeted for plano in the dominant eye were also included if the nondominant was myopic and had astigmatism ≤-2.50 D. Patients with visually significant ophthalmic pathology in either eye other than cataract were excluded.

The dominant eye is the eye the patients choose to look through a small aperture at a distance target. With contact lenses, patients were tested for tolerance to anisometropia of -1.50 D or more to determine their suitability for monovision. Surgical alternatives such as multifocal and extended depth of focus IOLs and monovision with single focus IOLs were offered.

All operations were performed under local anesthesia by a single surgeon. The nondominant eyes were targeted for a refractive outcome of -1.00 D to -1.25 D, which is more myopic than that in other studies,[4,5] for better unaided near vision. The dominant eyes were targeted for plano to -0.25 D. The IOL Master Series 700 and the Barrett Universal II formula were used to calculate the IOL power required. Toric IOLs were selected for patients with astigmatism of ≥0.50 D in the dominant eye. The toric power and axis were determined by keratometry and OCULUS Pentacam (OCULUS Optikgeräte, Wetzlar, Germany). The nondominant eyes were implanted with IC-8 IOLs, whereas the dominant eyes were implanted with aspheric monofocal or monofocal toric IOLs. Self-sealing wounds (without sutures) were 3 mm in width for IC-8 and Abbott Medical Optics ZA9003 IOLs and 2.4 mm for other IOLs. The surgical wounds were made in the plus axis of the astigmatism. Phacoemulsification was performed with the Alcon Centurion Vision System. The toric IOLs were aligned with the Alcon Verion Image guided system. The IOLs were implanted into the capsular bag. Postoperatively, topical chloramphenicol and prednisolone acetate 1% eyedrops were provided for 4 to 8 weeks to prevent inflammation and infection.

After 3 months, neodymium-yttrium-aluminum garnet laser capsulotomy was performed for posterior capsular opacification in patients with visual disturbances or decreased visual acuity secondary to posterior capsular opacification.

At 6 months, uncorrected distance, intermediate (60 cm), and near (40 cm) visual acuities (UDVA, UIVA, and UNVA, respectively) were measured on a Snellen-like chart at 6 m (for UDVA) or a Jaeger chart (for UIVA and UNVA). The smallest J number read was converted to logMAR for analysis.

At 6 to 9 months, the self-administered 30-item Quality of Vision questionnaire[9] was used to assess presence of visual symptoms related to dysphotopsias. Patients were asked to score 10 dysphotopsia symptoms (glare, haloes, starbursts, hazy vision, blurred vision, distortion, double or multiple images, fluctuating vision, focusing difficulties, and difficulty judging distances or depth) in terms of frequency (never, occasionally, quite often, or very often), severity (not at all, mild, moderate, or severe), and bothersomeness (not at all, a little, quite, or very). Scores are converted to range from 0 to 100; higher scores indicate worse quality of vision. In addition, patients were asked to rate their dependency on reading glasses (none, a little, moderate, or a great deal) and their satisfaction with vision in bright and dim light (very satisfied, satisfied, neutral, dissatisfied, or very dissatisfied).

Defocus curves were generated by plotting logMAR visual acuity against diopter of defocus based on refractive error. Visual acuities between eyes with IC-8 IOLs and eyes with monofocal IOLs were compared.

Results

Medical records of 15 men and 10 women aged 28 to 79 (mean, 60.8±11.5) years of Chinese (n=16), Caucasians (n=8), and South Asian (n=1) ethnicity were reviewed. Preoperative spherical equivalents for the nondominant and dominant eyes of the patients are shown in **Table 1**. Four of them had previous cataract surgery for the dominant eye with a monofocal IOL for plano implanted. In the dominant eyes, IOLs used included Rayner aspheric nontoric (n=12), Millennium Biomedical PreciSal toric (n=7) and PreciSal nontoric (n=4), Abbott Medical Optics ZA9003 (n=1), and Bausch and Lomb Akreos AO (n=1). Neodymium-yttrium-aluminum garnet laser capsulotomy for posterior capsular opacity was performed for 18 (72%) eyes with IC-8 IOLs and 12 (48%) eyes with monofocus IOLs (p=0.08).

Table 1. Preoperative spherical equivalent of the nondominant and dominant eyes of patients

Preoperative spherical equivalent, diopters	Nondominant eye	Dominant eye
	No. of patients	
0 to <-1	4	7
-1 to <-2	6	4
-2 to <-3	2	5
-3 to <-4	7	3
-4 to <-5	2	4
-5 to <-6	2	0
>-6	2	2

At 6 months, the mean spherical equivalent improved from -2.92±1.88 D to -1.20±0.47 (range, -0.25 to -2.125) D in nondominant eyes and from -2.42±1.82 D to -0.13±0.22 (range +0.25 to -0.50) D in dominant eyes, whereas the mean astigmatism improved from -0.86±0.67 (range, 0.00 to -2.50) D to -0.35±0.41 (range, 0.00 to -1.50) D in nondominant eyes (p=0.001) and from -0.76±0.53 (range, 0 to -1.75) D to -0.19±0.30 (range, 0.00 to -0.75) D in dominant eyes. UDVA tended to be better in eyes with monofocal IOLs (p<0.001), whereas UIVA and UNVA tended to be better with IC-8 IOLs (both p<0.001) [**Table 2**].

Defocus curves of a representative patient is shown in **Figure 2**. At the 0.20 logMAR (N5) threshold, the eye with the IC-8 IOL had a range of 3.50 D, compared with a range of 1.50 D in the eye with the monofocal IOL. With refraction of -1.50 D in the eye with the IC-8 IOL, the patient could read at 30 cm at an acuity of 0.20 logMAR.

20 (80%) patients reported never or occasionally experiencing dysphotopsia symptoms; 20 (80%) patients reported not at all or mild severity of symptoms; and 21 (84%) patients reported not at all or little bothersomeness of symptoms (**Table 3**). The mean score was 32.1 for frequency, 25.4 for severity, and 23.9 for bothersomeness. No patient had adverse effect or complication. For dependency on reading glasses, 40% had none, 36% a little, 12% moderate, and 12% a great deal. For satisfaction with vision in bright and dim light, respectively, 4% and 24% were dissatisfied, 12% and 20% neutral, and 84% and 56% satisfied or very satisfied. No patients were very dissatisfied.

Discussion

Patients with myopia are often dissatisfied with reduced unaided near vision after cataract surgery targeting for plano. This may be improved by the use of trifocal IOLs, extended depth of focus IOLs, or monofocal IOLs targeting distance vision for the dominant eye and intermediate/near vision for the nondominant eye (ie, monovision). The optimal anisometropia is approximately 1.50 D, and the refractive target for the nondominant eye is -1.50 D.[10,11] However, monovision has several disadvantages: (1) blur in the nondominant eye for distance and the dominant eye for near, (2) reduced stereopsis, (3) myopia of -1.5 D is often inadequate for clear unaided vision closer than 40 cm, and (4) nocturnal dysphotopsia. In the present study, 92% and 100% of patients achieved binocular UDVA of 20/20 and binocular UNVA of N5 (0.2 logMAR), which are better than the 68% and 56%, respectively, reported in a study of pseudophakic monovision.[11]

Table 2. Uncorrected distance, intermediate (60 cm), and near (40 cm) visual acuity of the nondominant, dominant, and both eyes at 6 months

LogMAR	Nondominant eye (with IC-8 intraocular lens)	Dominant eye (with monofocal intraocular lens)	Binocular
	% of patients		
Uncorrected distance visual acuity			
>0.18 to ≤0.30	24	4	0
>0.10 to ≤0.18	44	8	8
>0.00 to ≤0.10	12	8	0
≤0.00	20	80	92
Uncorrected intermediate visual acuity			
>0.30	0	56	0
>0.18 to ≤0.30	0	12	8
>0.10 to ≤0.18	4	12	4
>0.00 to ≤0.10	24	20	24
≤0.00	72	0	64
Uncorrected near visual acuity			
>0.50	0	76	0
>0.40 to ≤0.50	0	16	0
>0.30 to ≤0.40	0	8	0
>0.20 to ≤0.30	0	0	0
≤0.20	100	0	100

The IC-8 IOL can enhance monovision by increasing the depth of focus in the nondominant eye. This decreases the sensation of blur and improves stereopsis.

In the present study, the refractive target was -1.00 D to -1.25 D (compared with -0.75 D in two previous studies[4,5]) in nondominant eyes with IC-8 IOLs, because patients were myopic and accustomed to good unaided near vision. In the present study, 100% of patients achieved binocular UDVA of 0.2 logMAR, compared with the 99%[4] and 98%[5], whereas 92% of patients achieved binocular UIVA of 0.2 logMAR, compared with 95%[4] and 83%[5] in two previous studies, and 100% of patients achieved binocular UNVA of 0.2 logMAR (N5), compared with 79%[4] and 76.2%[5] in two previous studies. In the present study, postoperatively, 40% of patients did not wear glasses at all and 36% of patients wore glasses for a small amount of time when ambient light was poor, compared with 54% of patients who were 'glasses independent'.[5] The difference may be due to the inclusion of both myopic and hypermetropic patients in the previous study.[5]

The defocus curves of a representative patient support the improved near vision with a greater myopic refractive target. The eye with the monofocal IOL had a range of 1.50 D at 0.2 logMAR (N5) acuity, whereas the eye with the IC-8 IOL had a range of 3.5 D at 0.2 logMAR acuity. With the IC-8 IOL, a refraction of -0.75 D provides 0.2 logMAR acuity at 40 cm, whereas a refraction of -1.25 D provides 0.2 logMAR acuity at 33 cm. A patient tolerant of 1.5 D of anisometropia can accept -1.25–D target with the IC-8 IOL in the nondominant eye, which provides up to 7 cm of increased close range compared with the -0.75–D target.

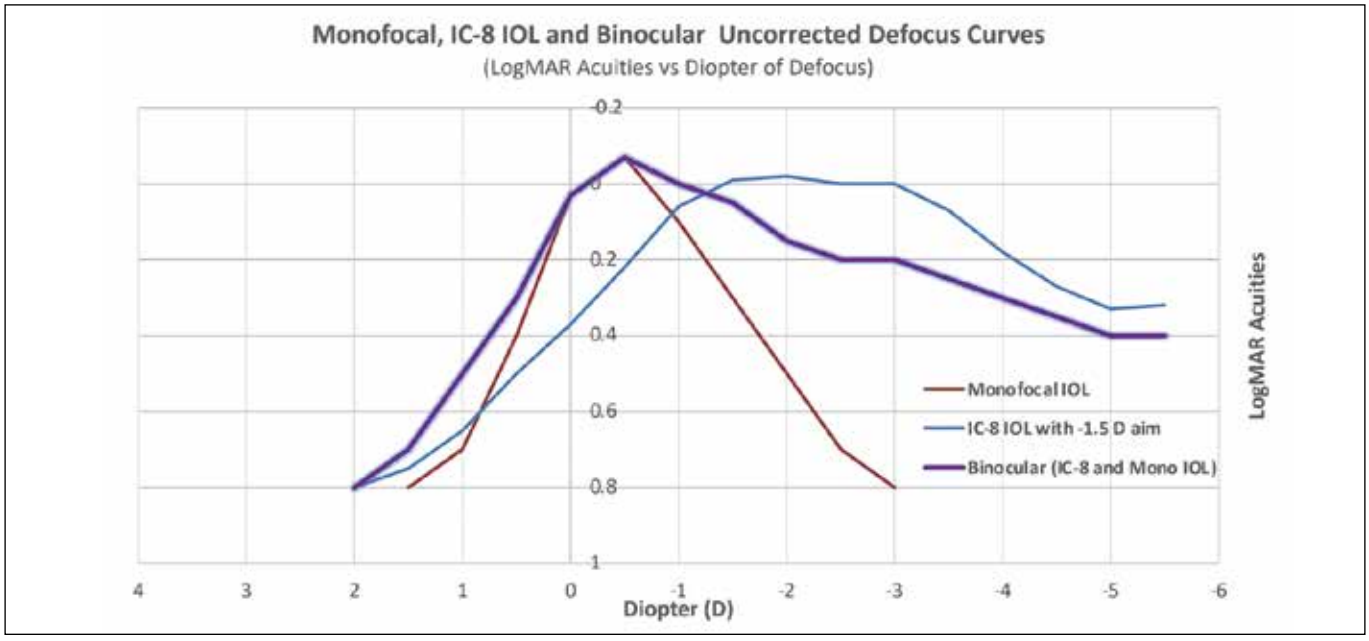


Figure 2. Defocus curves in a representative patient: at the 0.20 logMAR (N5) threshold, the eye with the IC-8 intraocular lens (IOL) has a range of 3.50 diopters, whereas the eye with the monofocal intraocular lens has a range of 1.50 diopters. Binocularly, 0.20 logMAR acuity is maintained across 3.50 diopters from +0.50 diopter to -3.00 diopters.

Table 3. Frequency, severity, and bothersomeness of symptoms based on the Quality of Vision questionnaire

Symptom	None / not at all	Occasionally / mild	Quite often / moderate	Very often / severe
	% of patients			
Glare				
Frequency	36	56	8	0
Severity	40	44	16	0
Bothersomeness	44	48	8	0
Haloes				
Frequency	68	20	8	4
Severity	72	20	8	0
Bothersomeness	72	28	0	0
Starbursts				
Frequency	56	32	12	0
Severity	56	32	12	0
Bothersomeness	64	28	8	0
Hazy vision				
Frequency	68	28	4	0
Severity	76	20	4	0
Bothersomeness	76	20	4	0
Blurred vision				
Frequency	64	32	4	0
Severity	68	28	4	0
Bothersomeness	68	28	0	4
Distortion				
Frequency	100	0	0	0
Severity	100	0	0	0
Bothersomeness	100	0	0	0
Double/multiple images				
Frequency	84	16	0	0
Severity	84	16	0	0
Bothersomeness	96	4	0	0
Fluctuating vision				
Frequency	56	36	8	0
Severity	60	36	4	0
Bothersomeness	76	16	8	0
Focusing difficulties				
Frequency	36	60	4	0
Severity	44	52	4	0
Bothersomeness	52	44	4	0
Difficulty judging distances or depth				
Frequency	68	28	4	0
Severity	72	28	0	0
Bothersomeness	80	20	0	0

Compared with unilateral implantation, bilateral implantation of the IC-8 IOL was reported to achieve better intermediate and near vision but lower patient satisfaction and more dysphotopsias.[12] However, in another study, no significant difference was reported in patient satisfaction between bilateral and unilateral implantation of IC-8 IOL.[13] Disadvantages of bilateral implantation of the IC-8 IOL are poorer binocular vision in dim light and increased nocturnal dysphotopsias, as 24% of our patients were dissatisfied with vision in dim light (compared to 4% in bright light).

The Quality of Vision questionnaire has been used to examine the effects of various IOLs on visual performance.[14-16] The AT LISA 809M was reported to have Rasch-adjusted mean scores of 27, 21, and 16 for frequency, severity, and bothersomeness of dysphotopsia symptoms, respectively, whereas the respective scores for the AcrySof ReSTOR SN6AD1 were 28, 22, and 19.[14] In the present study, the respective scores were higher at 32, 25, and 24. The higher scores are likely due to differences in study populations, as the present study included patients with myopia only and the others not.

The rate of posterior capsulotomy was higher in eyes with the IC-8 IOL than in eyes with the monofocal IOL at 6 months (72% vs 48%, p=0.08), and was higher than the 31.1% for hydrophilic IOLs and 7.1% for hydrophobic IOLs in one study.[17] As the small aperture lens directs light through the small central opening, the quality and clarity of the central capsule behind the aperture becomes more significant. In eyes with the IC-8 IOL, slight opacities and folds in the capsule behind the aperture may affect vision more quickly and necessitate earlier laser capsulotomy. The IC-8 IOL is made from hydrophobic acrylic material with <4% water content, and the posterior surface has a 360-degree square edge. Both features should reduce posterior capsular opacification.

Contraindications of the IC-8 IOL are those with active retinal disease, uncontrolled glaucoma, microphthalmia, chronic uveitis, corneal dystrophy, corneal endothelial dysfunction, and those aged <18 years. Those with mesopic size of >5.6 mm should not use the IC-8 IOL, as light may enter the eye outside of the opaque ring and cause dysphotopsias.[4,12]

Limitations to the present study are the small sample size, the lack of controls, and the retrospective nature. Generalization of our findings to wider populations may not be feasible. Larger prospective randomized controlled studies are warranted to compare postoperative unaided visual acuity and quality of vision in different patients including those with myopia, hypermetropia, and emmetropia. Comparison should be made between different levels of monovision with the IC-8 IOL and with bilateral multifocal IOLs.

Conclusion

The IC-8 IOL is a good option for patients with myopia who can tolerate monovision. It enhances monovision by

extending the depth of focus at near range and binocularity at distance when lighting is adequate. Patients who plan to have the IC-8 IOL implanted in the nondominant eye should be counseled about vision in dim light and the presence of dysphotopsias.

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

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

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

References

1. *Roberts TV, Lawless M, Chan CC, et al. Femtosecond laser cataract surgery: technology and clinical practice. Clin Exp Ophthalmol 2013;41:180-6.* Crossref
2. *Abell RG, Kerr NM, Vote BJ. Toward zero effective phacoemulsification time using femtosecond laser pretreatment. Ophthalmology 2013;120:942-8.* Crossref
3. *Dexl AK, Jell G, Strohmaier C, et al. Long-term outcomes after monocular corneal inlay implantation for the surgical compensation of presbyopia. J Cataract Refract Surg 2015;41:566-75.* Crossref
4. *Dick HB, Piovella M, Vukich J, Vilupuru S, Lin L; Clinical Investigators. Prospective multicenter trial of a small-aperture intraocular lens in cataract surgery. J Cataract Refract Surg 2017;43:956-68.* Crossref
5. *Hooshmand J, Allen P, Huynh T, et al. Small aperture IC-8 intraocular lens in cataract patients: achieving extended depth of focus through small aperture optics. Eye (Lond) 2019;33:1096-103.* Crossref
6. *Agarwal S, Thornell EM. Cataract surgery with a small-aperture intraocular lens after previous corneal refractive surgery: visual outcomes and spectacle independence. J Cataract Refract Surg 2018;44:1150-4.* Crossref
7. *Shajari M, Mackert MJ, Langer J, et al. Safety and efficacy of a small-aperture capsular bag-fixated intraocular lens in eyes with severe corneal irregularities. J Cataract Refract Surg 2020;46:188-92.* Crossref
8. *Sánchez-González JM , Sánchez-González MC , De-Hita-Cantalejo C, Ballesteros-Sánchez A. Small aperture IC-8 extended-depth-of-focus intraocular lens in cataract surgery: a systematic review. J Clin Med 2022;11:4654.* Crossref
9. *McAlinden C, Pesudovus K, Moore JE. The development of an instrument to measure quality of vision: the Quality of Vision (QoV) questionnaire. Invest Ophthalmol Vis Sci 2010;51:5537-45.* Crossref
10. *Hayashi K, Yoshida M, Manabe S, Hayashi H. Optimal amount of anisometropia for pseudophakic monovision. J Refract Surg 2011;27:332-8.* Crossref
11. *Finkelman YM, Ng JQ, Barrett GD. Patient satisfaction and visual function after pseudophakic monovision. J Cataract Refract Surg 2009;35:998-1002.* Crossref
12. *Dick HB, Elling M, Schultz T. Binocular and monocular implantation of small-aperture intraocular lenses in cataract surgery. J Refract Surg 2018;34:629-31.* Crossref
13. *Ang RE, Picache GCS, Rivera MCR, Lopez LRL, Cruz EM. A comparative evaluation of visual, refractive, and patient-reported outcomes of three extended depth of focus (EDOF) intraocular lenses. Clin Ophthalmol 2020;14:2339-51.*
14. *Maurino V, Allan BD, Rubin GS, et al. Quality of vision after bilateral multifocal intraocular lens implantation: a randomized trial—AT LISA 809M versus AcrySof ReSTOR SN6AD1. Ophthalmology 2015;122:700-10.* Crossref
15. *Ribeiro FJ, Ferreira TB. Comparison of visual and refractive outcomes of 2 trifocal intraocular lenses. J Cataract Refract Surg 2020;46:694-9.* Crossref
16. *Monaco G, Gari, Di Censo F, Poscia A, Ruggi G, Scialdone A. Visual performance after bilateral implantation of 2 new presbyopia-correcting intraocular lenses: trifocal versus extended range of vision. J Cataract Refract Surg 2017;43:737-47.* Crossref
17. *Auffarth GU, Brezin A, Caporossi A, et al. Comparison of Nd: YAG capsulotomy rates following phacoemulsification with implantation of PMMA, silicone, acrylic intra-ocular lenses in four European countries. Ophthalmic Epidemiol 2004;11:319-29.* Crossref

ORIGINAL ARTICLE

Artificial intelligence to detect referable diabetic retinopathy in a Chinese population in Hong Kong

Sunny Chi Lik Au[1,2], MBChB, MRCSEd, FCOphthHK; George Tsz Ho Shum[3], MBBS, MRCP(UK); Steffi Shing Yee Chong[1,2], MBBS; Callie Ka Li Ko[1,2], MBBS, FCOphthHK, FHKAM (Ophthalmology)
[1]*Department of Ophthalmology, Tung Wah Eastern Hospital, Hong Kong SAR, China*
[2]*Department of Ophthalmology, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China*
[3]*Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China*

Correspondence and reprint requests:
Dr Sunny Chi Lik Au, 9/F, MO Office, Tung Wah Group of Hospitals 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 aimed to investigate the sensitivity and specificity of the Deep Fundus, an artificial intelligence program for diabetic retinopathy screening, in Chinese patients with diabetes.

Methods: Fundus photographs of Chinese patients with diabetes aged 50 to 90 years who attended Pamela Youde Nethersole Eastern Hospital, Hong Kong between December 2020 and June 2021 during the public diabetic retinopathy screening period were retrospectively retrieved in February 2022. Two ophthalmologists independently graded the fundus photographs for diabetic retinopathy (according to the recommendations in the 2017 International Council of Ophthalmology Guidelines for Diabetic Eye Care) and any concomitant eye pathology such as cataracts or macular diseases. On 27 February 2022, the photographs were uploaded to the Deep Fundus website. Fundus images were classified into referable or non-referable diabetic retinopathy in accordance with the abovementioned Guidelines. Sensitivity and specificity of the Deep Fundus were determined.

Results: Of 202 eyes screened, 96 eyes were included in the analysis. There was no discordance between the two ophthalmologists in the diabetic retinopathy gradings. 57 (59.4%) eyes were graded to have positive diabetic retinopathy findings. Using gradings of the two ophthalmologists as the gold standard, sensitivity and specificity of the Deep Fundus were 62.3% and 90.7%, respectively. The positive and negative predictive values were 89.2% and 66.1%, respectively.

Conclusions: The sensitivity and specificity of the Deep Fundus for diabetic retinopathy screening in a Chinese population were 62.3% and 90.7%, respectively. Further real-world validation studies are needed to assess the artificial intelligence model, particularly among Chinese patients with cataracts, myopia, diabetic macular edema, or proliferative diabetic retinopathy.

Key words: Artificial intelligence; Diabetic retinopathy; East Asian people; Machine learning; Sensitivity and specificity

Introduction

Big data and machine learning are transforming healthcare. Artificial intelligence (AI) and deep learning have trained a wide range of computer models for medical triage and diagnostic testing.[1] AI has comparable performance to medical personnel in certain fields and may offer solutions to overburdened healthcare services resulting from an aging population and a shortage of healthcare personnel.[2,3]

Among commercially available AI products for ophthalmology,[4,5] analysis of fundus photographs[6] and optical coherence tomography images[7] remains the core technologies. Two AI systems for diabetic retinopathy

(DR) screening have been approved by the United States Food and Drug Administration for marketing.[8] AI screening for age-related macular degeneration and glaucoma are developing as well.[6]

The International Diabetes Federation estimated that the global diabetic prevalence was 9.3% (equaling 463 million people) in 2019.[9] The concept of DR screening began in 1989 with the St Vincent Declaration, which aimed to reduce diabetes mellitus (DM)–related blindness by one-third in 5 years.[10] DR screening aims to detect important, treatable pathology in its early stages with a low-cost, efficient, and non-invasive diagnostic test.[11] In Hong Kong, DR screening is performed by primary care physicians, endocrinologists, optometrists, or specially-trained graders with non-stereoscopic digital color retinal fundus photographs.[11] Most AI models were validated in Caucasian populations, but the algorithm may differ in Chinese populations. For instance, Chinese populations have a higher prevalence of myopia than Caucasian populations. Therefore, this study aimed to investigate the sensitivity and specificity of the Deep Fundus, an AI program for DR screening, in Chinese patients with diabetes.

Materials and methods

Fundus photographs of patients with diabetes who attended a public DR screening at Pamela Youde Nethersole Eastern Hospital, Hong Kong, between December 2020 and June 2021 were retrospectively retrieved in February 2022, with patient identifiers removed. All fundus photographs were taken by the Non-Mydriatic Auto Fundus Camera AFC-330 (Nidek, Gamagori, Japan). Two photographs were taken per eye: one centered on the macula and the other centered on the optic disc.[12] Photographs of all sorts of quality were included to reflect the real-world situation of dense cataracts or different media opacities. Patients aged <50 years and >90 years were excluded to comply with the age range defined by the Deep Fundus.[13] Non-Chinese patients were excluded, as were patients with branch retinal vein occlusion, age-related macular degeneration, retinal macroaneurysm, or missing fundus photographs.

Two ophthalmologists specializing in vitreoretinal diseases who were blinded from patient data independently graded the fundus photographs for DR (according to the recommendations in the 2017 International Council of Ophthalmology Guidelines for Diabetic Eye Care)[14] and any concomitant eye pathology such as cataracts or macular diseases.

The Deep Fundus is accessible at www.deepfundus.com and is trained in the Eyetelligence (also available online),[13,15] which has been approved as a Class I medical device for clinical use in the European Union, United Kingdom, Australia, and New Zealand.[16-19] On 27 February 2022, the photographs were uploaded to the Deep Fundus website. Items investigated included valid fundus image, laterality, referable DR, DR severity scale, diabetic macular edema, and cataracts. Only eyes with valid fundus image and laterality were included in the sensitivity and specificity analysis. Fundus images were classified into referable or non-referable DR in accordance with the recommendations in the 2017 International Council of Ophthalmology Guidelines for Diabetic Eye Care.[14]

The sample size needed to determine the model's accuracy was calculated based on its sensitivity and specificity.[20,21] We searched PubMed, MEDLINE, Embase, and Scopus but found no previous publication on the performance of Deep Fundus on DR screening; therefore, we assumed the sensitivity and specificity to be 95% as claimed by the Deep Fundus. We first calculated the true positive (TP) + false negative (FN) for sensitivity and the true negative (TN) + false positive (FP) as follows:

$$TP+FN=Z^2\times[\text{sensitivity}\times(1-\text{sensitivity})/W^2]$$

$$TN+FP=Z^2\times[\text{specificity}\times(1-\text{specificity})/W^2]$$

where Z is set to 1.96 for the normal distribution value, corresponding to the 95% confidence interval (CI), and W, the maximum acceptable width of the 95% CI, is set to 10%.[20] The sample size calculations for sensitivity and specificity were TP+FN/P and TN+FP/(1−P), respectively, in which P is the prevalence of DR in the Chinese population in Hong Kong. In a previous study involving 174 532 patients, the estimated prevalence of DR was 39%.[11] Thus, 47 and 30 eyes were required for determining sensitivity and specificity, respectively, with a total of 77. Statistical analyses were performed using SPSS (Windows version 27.0; IBM Corp, Armonk [NY], USA).

Results

Of 202 eyes screened during the public DR screening period, 106 eyes were excluded owing to missing fundus photographs (n=1), non-Chinese ethnicity (n=14), or age <50 years (n=91), whereas 96 eyes in patients aged 50 to 77 (mean, 58.3±7.8) years were included in the analysis. The male-to-female ratio was 1.29:1. All eyes were graded correctly on laterality by the Deep Fundus.

There was no discordance between the two ophthalmologists in the DR gradings. 12 (12.5%) eyes were determined to be myopic according to the grading system by the meta-analysis for pathologic myopia study group.[22] 57 (59.4%) eyes were graded to have positive DR findings (**Table 1**). Five (5.2%) eyes had a history of pan-retinal photocoagulation laser treatment. No eye had vitreous, pre-retinal, or subhyaloid hemorrhages. One (1.0%) eye had tractional retinal detachment. Nine eyes with proliferative DR had neovascularization at disc or elsewhere. Fundus photograph quality was suboptimal in 26 (27.1%) eyes owing to cataracts. When macular details and the entire posterior pole of the fundus were obscured, efforts were made to grade the periphery. Nine (9.4%) eyes had macular diseases other than diabetic macular edema including dry age-related macular degeneration, myopic maculopathy, choroidal naevus, chorioretinal scars, and retinal artery macroaneurysms.

Table 1. Diabetic retinopathy (DR) characteristics of eyes according to the recommendations in the 2017 International Council of Ophthalmology Guidelines for Diabetic Eye Care (n=96)

Classification	No. of patients	Referable
No apparent DR	39	No
Mild non-proliferative DR	4	No
Moderate non-proliferative DR	33	Yes
Severe non-proliferative DR	3	Yes
Proliferative DR	9	Yes
Diabetic macular edema	9	Yes
Ungradable (treated proliferative DR or unclear fundus photo)	8	Yes

Table 2. Referable diabetic retinopathy (DR) grading according to the Deep Fundus and ophthalmologists

Referable DR grading by the Deep Fundus	Referable DR grading by ophthalmologists	
	Yes	No
Yes	33	4
No	20	39

Numbers of referable DR according to the Deep Fundus and the two ophthalmologists are shown in **Table 2**. Using gradings of the two ophthalmologists as the gold standard, sensitivity and specificity of the Deep Fundus were 62.3% (95% CI=47.9%-75.2%) and 90.7% (95% CI=77.9%-97.4%), respectively. The positive and negative predictive values were 89.2% (95% CI=76.0%-95.6%) and 66.1% (95% CI=57.7%-73.6%), respectively. **Figure 1** shows fundus photographs of true positive and true negative grading, whereas **Figure 2** shows fundus photographs of false positive and false negative grading.

Discussion

The Deep Fundus has a high specificity but a low sensitivity for detecting referable DR in Chinese patients with diabetes aged 50 to 90 years. To the best of our knowledge, this study is the first to investigate the clinical application of the Deep Fundus in Chinese populations. We used real-world data from a 7-month public screening service. The number of eyes studied (n=96) was well above the minimum required sample size. All diagnostic results from the Deep Fundus were generated on the same day (27 February 2022); this may eliminate potential bias from the ongoing update or learning of the AI model. The Deep Fundus is only valid for patients aged 50 to 90 years; 45.0% (n=91) of eyes in patients aged <50 years were excluded; some of these patients had type 1 DM and/or gestational DM.

Disease prevalence affects the sample size calculation for determining the sensitivity and specificity of a diagnostic test.[20,21] We used the DR prevalence of 39% in primary care settings[11] to calculate the sample size, but the present study had a higher prevalence of DR at 59.4%. This is expected among patients in ophthalmology and internal medicine departments of a tertiary-level hospital. Consequently, DM cases were more complicated and severe than those typically encountered in primary care settings. Using the prevalence of 59.4% in the sample size calculation, the numbers of eyes required for sensitivity and specificity would be 31 and 45, respectively, and the minimum sample size would be 76. Therefore, our study is powered to demonstrate the real-world sensitivity and specificity of the Deep Fundus.

DM is a risk factor for the development of cataracts, and the prevalence of cataracts in DM patients ranges from 20% to 66%.[23,24] In our study, 27.1% of our DM patients had a visually significant cataract affecting the quality of their fundus photographs. However, the sample size of patients with cataracts was too small for subgroup analysis. Possible confounding factors include the variable severity of cataracts and the retrospective study design, which could introduce

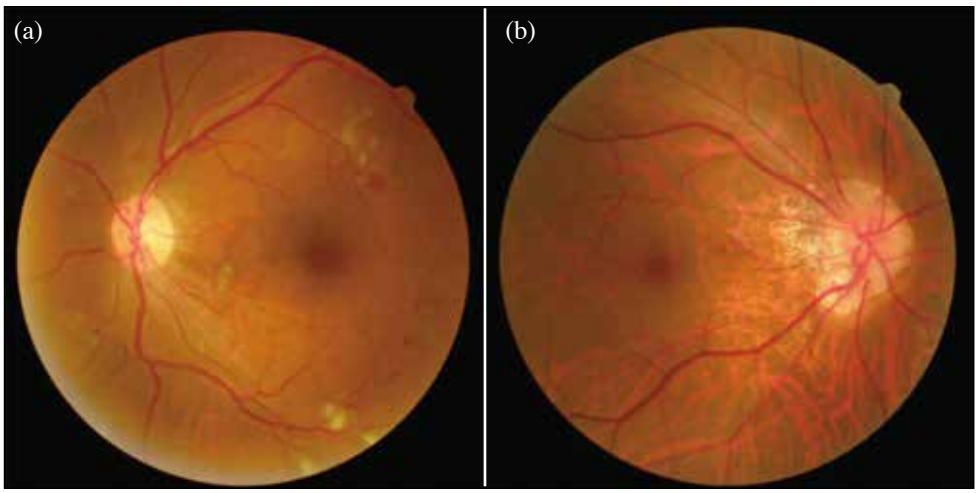


Figure 1. Fundus photographs showing (a) true positive and (b) true negative referable diabetic retinopathy grading by the Deep Fundus, which is graded as myopia by ophthalmologists.

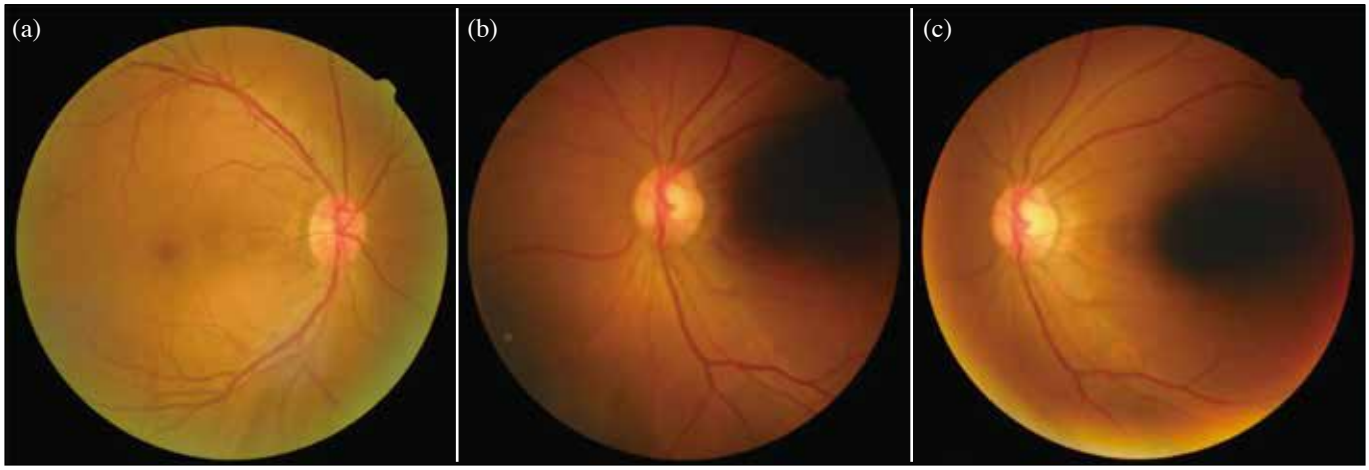


Figure 2. (a) A fundus photograph showing false positive referable diabetic retinopathy grading by the Deep Fundus. Only microaneurysms are seen, with no macular edema. This is graded as mild non-proliferative diabetic retinopathy by ophthalmologists but as moderate non-proliferative diabetic retinopathy by the Deep Fundus. (b and c) Fundus photographs showing a false negative referable diabetic retinopathy grading by the Deep Fundus. Cataracts obscure the macula; this patient should be referred according to the ophthalmologists.

selection bias. The quality of the fundus images can be a confounding factor for the Deep Fundus performance. We included photographs of varying quality to reflect the real-world situation of cataracts or different causes of media opacities. However, the prevalence and severity of media opacities differ across different populations with different demographics.[25] This variation would affect the sensitivity and specificity of the Deep Fundus in clinical practice.

The United States Food and Drug Administration has approved two AI systems for DR screening: the IDx-DR (Digital Diagnostics, Coralville [IA], USA) and EyeArt (Eyenuk, Woodland Hills [CA], USA), both of which have sensitivity and specificity approaching 90% as demonstrated in large-scale studies.[26-28] Other AI systems to assess DR are also available.[29] Retmarker DR (Retmarker, Coimbra, Portugal) has been certified as a Class IIa medical device in Europe.[30] In China, AI-based software for DR includes Airdoc (Beijing, China).[31] When adopting AI systems in clinical settings in Hong Kong, the algorithms should ideally be trained by photographs of Asian/Chinese eyes. The low sensitivity (62.3%) of the Deep Fundus suggests a considerable number of false negative cases of referable DR, which might progress rapidly to more severe grades of DR that are not timely detected by annual screening. Therefore, we suggest manually reviewing all negative cases graded by Deep Fundus to avoid missing the golden period of referral to ophthalmologists for monitoring. Nonetheless, if there are AI models with higher sensitivity, a semi-automated model can be considered in Hong Kong, in which retinal photographs initially analyzed by an AI model to filter out non-referable DR cases, followed by grading by ophthalmologists. Such models have been used in the UK and Singapore.[32]

Refraction status can change after corneal refractive or cataract surgery. Some of our patients have pseudophakia, and the axial length measurement was not available. Thus, fundus photographs were used to determine myopia. According to the meta-analysis for pathologic myopia study group,[22] visible signs of myopia on fundus photographs include a tessellated fundus, diffuse chorioretinal atrophy, patchy chorioretinal atrophy, macular atrophy, lacquer cracks, myopic choroidal neovascularization, and Fuchs spots. Some of these may mimic DR. For example, myopic choroidal neovascularization or lacquer cracks can be misinterpreted as DR hemorrhages, given that all present as red dots. Similarly, chorioretinal atrophy can be misinterpreted as exudate given that both are white in color. However, the prevalence of myopia in our patients was 12.5%, which is lower than the 41.1% reported in other studies in Asia.[33,34] Subgroup analysis of myopic patients was not possible because of the small sample size (n=12).

Conclusion

The sensitivity and specificity of the Deep Fundus for DR screening in a Chinese population were 62.3% and 90.7%, respectively. Further real-world validation studies are needed to assess the AI model, particularly among Chinese patients with cataracts, myopia, diabetic macular edema, or proliferative DR.

Contributors

SCLA designed the study; all authors acquired the data; SCLA and GTHS analyzed the data; SCLA drafted the manuscript; and SCLA 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 an editor of the journal, SCLA was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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 Hong Kong East Cluster Research Ethics Committee (Reference: HKEC-REC-2022-019). The patients were treated in accordance with the tenets of the Declaration of Helsinki.

References

1. *Marchiori C, Dykeman D, Girardi I, et al. Artificial intelligence decision support for medical triage. AMIA Annu Symp Proc 2021;2020:793-802.*
2. *Baker A, Perov Y, Middleton K, et al. A comparison of artificial intelligence and human doctors for the purpose of triage and diagnosis. Front Artif Intell 2020;3:543405.* Crossref
3. *Lee D, Yoon SN. Application of artificial intelligence–based technologies in the healthcare industry: opportunities and challenges. Int J Environ Res Public Health 2021;18:271.* Crossref
4. *Bali J, Bali O. Artificial intelligence in ophthalmology and healthcare: an updated review of the techniques in use. Indian J Ophthalmol 2021;69:8-13.* Crossref
5. *Goldhagen BE, Al-Khersan H. Diving deep into deep learning: an update on artificial intelligence in retina. Curr Ophthalmol Rep 2020;8:121-8.* Crossref
6. *Zapata MA, Royo-Fibla D, Font O, et al. Artificial intelligence to identify retinal fundus images, quality validation, laterality evaluation, macular degeneration, and suspected glaucoma. Clin Ophthalmol 2020;14:419-29.* Crossref
7. *Kapoor R, Whigham BT, Al-Aswad LA. Artificial intelligence and optical coherence tomography imaging. Asia Pac J Ophthalmol (Phila) 2019;8:187-94.*
8. *Lim G, Bellemo V, Xie Y, Lee XQ, Yip MYT, Ting DSW. Different fundus imaging modalities and technical factors in AI screening for diabetic retinopathy: a review. Eye Vis (Lond) 2020;7:21.* Crossref
9. *Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843.* Crossref
10. *Diabetes care and research in Europe: the Saint Vincent declaration. Diabet Med 1990;7:360.* Crossref
11. *Gangwani RA, Lian JX, McGhee SM, Wong D, Li KK. Diabetic retinopathy screening: global and local perspective. Hong Kong Med J 2016;22:486-95.* Crossref
12. *Gangwani R, Lai WW, Sum R, et al. The incidental findings of age-related macular degeneration during diabetic retinopathy screening. Graefes Arch Clin Exp Ophthalmol 2014;252:723-9.* Crossref
13. *Deep Fundus. Available from: https://www.deepfundus.com/*
14. *Wong TY, Sun J, Kawasaki R, et al. Guidelines on diabetic eye care: the International Council of Ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology 2018;125:1608-22.* Crossref
15. *Eyetelligence. Available from: https://eyetelligence.ai/us/.*
16. *Kiburg KV, Turner A, He M. Telemedicine and delivery of ophthalmic care in rural and remote communities: drawing from Australian experience. Clin Exp Ophthalmol 2022;50:793-800.* Crossref
17. *Keel S, Li Z, Scheetz J, et al. Development and validation of a deep-learning algorithm for the detection of neovascular age-related macular degeneration from colour fundus photographs. Clin Exp Ophthalmol 2019;47:1009-18.* Crossref
18. *Li Z, He Y, Keel S, Meng W, Chang RT, He M. Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs. Ophthalmology 2018;125:1199-206.* Crossref
19. *Li Z, Keel S, Liu C, et al. An automated grading system for detection of vision-threatening referable diabetic retinopathy on the basis of color fundus photographs. Diabetes Care 2018;41:2509-16.* Crossref
20. *Negida A, Fahim NK, Negida Y. Sample size calculation guide - Part 4: how to calculate the sample size for a diagnostic test accuracy study based on sensitivity, specificity, and the area under the ROC curve. Adv J Emerg Med 2019;3:e33.*
21. *Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med 1996;3:895-900.* Crossref
22. *Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. Am J Ophthalmol 2015;159:877-83.e7.* Crossref
23. *Pék A, Szabó D, Sándor GL, et al. Relationship between diabetes mellitus and cataract in Hungary. Int J Ophthalmol 2020;13:788-93.* Crossref
24. *Becker C, Schneider C, Aballéa S, et al. Cataract in patients with diabetes mellitus-incidence rates in the UK and risk factors. Eye (Lond) 2018;32:1028-35.* Crossref
25. *Lee AY, Yanagihara RT, Lee CS, et al. Multicenter, head-to-head, real-world validation study of seven automated artificial intelligence diabetic retinopathy screening systems. Diabetes Care 2021;44:1168-75.* Crossref
26. *van der Heijden AA, Abramoff MD, Verbraak F, van Hecke MV, Liem A, Nijpels G. Validation of automated screening for referable diabetic retinopathy with the IDx-DR device in the Hoorn Diabetes Care System. Acta Ophthalmol 2018;96:63-8.* Crossref

27. *Bhaskaranand M, Ramachandra C, Bhat S, et al. The value of automated diabetic retinopathy screening with the EyeArt system: a study of more than 100,000 consecutive encounters from people with diabetes. Diabetes Technol Ther 2019;21:635-43.* Crossref
28. *Ipp E, Liljenquist D, Bode B, et al. Pivotal evaluation of an artificial intelligence system for autonomous detection of referrable and vision-threatening diabetic retinopathy. JAMA Netw Open 2021;4:e2134254.* Crossref
29. *Li S, Zhao R, Zou H. Artificial intelligence for diabetic retinopathy. Chin Med J (Engl) 2021;135:253-60.* Crossref
30. *Tufail A, Kapetanakis VV, Salas-Vega S, et al. An observational study to assess if automated diabetic retinopathy image assessment software can replace one or more steps of manual imaging grading and to determine their cost-effectiveness. Health Technol Assess 2016;20:1-72.* Crossref
31. *Gu C, Wang Y, Jiang Y, et al. Application of artificial intelligence system for screening multiple fundus diseases in Chinese primary healthcare settings: a real-world, multicentre and cross-sectional study of 4795 cases. Br J Ophthalmol 2023:322940.* Crossref
32. *Cheung CY, Tang F, Ting DSW, Tan GSW, Wong TY. Artificial intelligence in diabetic eye disease screening. Asia Pac J Ophthalmol (Phila) 2019;8:158-64.*
33. *Mak CY, Yam JC, Chen LJ, Lee SM, Young AL. Epidemiology of myopia and prevention of myopia progression in children in East Asia: a review. Hong Kong Med J 2018;24:602-9.* Crossref
34. *Van Newkirk MR. The Hong Kong vision study: a pilot assessment of visual impairment in adults. Trans Am Ophthalmol Soc 1997;95:715-49.*

Amblyopia management

Gladys H Sit[1], MBBS; Emily S Wong[2,3], FRCOpth; Jason CS Yam[2,3,4], FRCOpth
[1]Princess Margaret Hospital, Hong Kong SAR, China
[2]Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China
[3]Hong Kong Eye Hospital, Hong Kong SAR, China
[4]Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong SAR, China

Correspondence and reprint requests:
Dr Jason CS Yam, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China. Email: yamcheuksing@cuhk.edu.hk

Abstract

Amblyopia is a reversible neurodevelopmental disorder but can cause vision loss if untreated, especially within critical period of visual neuroplasticity. We review different treatment modalities for amblyopia including refractive correction, occlusion therapy, medication, surgery, perceptual learning, and the more advanced binocular therapy. Binocular therapy can improve both visual acuity and stereoacuity, but whether it is superior to occlusion therapy remains controversial. Future studies to determine the optimal treatment duration, timing of initiation, dosage, and when to step-up treatment when other treatments become refractory are warranted.

Key words: Amblyopia; Vision, binocular; Visual acuity

Introduction

Amblyopia is a neurodevelopmental disorder resulting in abnormal visual acuity (VA) in one or both eyes.[1] Unilateral amblyopia is defined as VA difference of ≥2 lines on Snellen chart between eyes, whereas bilateral amblyopia is defined as VA of worse than 20/50, 20/40, and 20/30 in both eyes in children aged 3 to <4, 4 to ≤5, and >5 years, respectively.[2] Amblyopia is reversible but can cause vision loss if untreated. It affects approximately 1% to 4% of the population.[3] Early detection and management of amblyopia can maximize children's visual development potential.

Neuroplasticity

Early detection enables timely management during the period of greatest plasticity of visual cortex, which is the primary site of visual deficit in amblyopia.[4] Plasticity is a dynamic ability to functionally recognize external stimuli and structurally respond to them. This developmental mechanism relies heavily on the interaction of cortical afferent neurons between both eyes. Reduced connection in the deprived eye was due to competition with the non-deprived eye, rather than the disuse of the deprived eye.[5] Treatment should be started before the age of 7 years and can be extended beyond this age to reverse visual deficits such as reduced VA, stereoacuity, and contrast sensitivity as well as crowding and recurrence.[6-8]

Many patients with amblyopia are affected by reduced fine motor skills and oculomotor skills such as unsteady fixation, delayed initiation of saccades, and inaccurate tracking.[9] Amblyopia reduces the quality of life, as it affects school and career choices, self-esteem, social acceptance, and self-perception.[10]

Treatment

Treatment is guided by thorough history taking and physical examinations to identify any reversible underlying causes. Treatment modalities include optical refractive correction, occlusion therapy, medication, surgery, Bangerter filters, and the more advanced binocular visual stimulation and perceptual learning.

For optical refractive correction, the magnitude of anisometropia correlates with the degree of amblyopia. 20% of patients with a high refractive error develop vision loss secondary to amblyopia.[11] In patients with anisometropic amblyopia (with VA ranging from 20/40 to 20/250) treated with optical refractive correction until VA stabilized or amblyopia resolved, 77% of patients had improvement in VA by ≥2 lines and 27% of patients had resolution of anisometropic amblyopia.[12] However, those with severe amblyopia or higher degree of anisometropic amblyopia did

not respond well to refractive correction alone.

Occlusion therapy (patching) remains the mainstay treatment in Hong Kong after refractive correction.[13] By occluding the fellow eye, neural signal from the fellow eye is reduced and thus the amblyopic eye is allowed to be fully stimulated and forced to overcome the suppression from the fellow eye and activate its visual pathway. Patching is highly effective, with stable response until at least 15 years of age. In a Pediatric Eye Disease Investigator Group (PEDIG) study of the use of an opaque adhesive patch for 2 to 6 hours per day, with dosage adjusted according to the VA response of patients, visual outcomes were similar between 2 hours and 6 hours of occlusion therapy in children aged 3 to 7 years with moderate amblyopia.[14] VA improved by ≥3 lines after 4 months of patching in 62% of patients in both 2-hour and 6-hour groups. Parents of the 6-hour group expressed more concern over social stigma that may lead to lower compliance. Patching can be used in older children and adolescents, particularly those who are treatment naive.[15] Drawbacks of patching include local irritation, allergy, cosmetic impact, reverse amblyopia, and low compliance. Recurrence amblyopia is common, especially in those with severe amblyopia. Thus, gradual tapering of patching is preferable to an abrupt cessation of therapy.[16]

Medication treatment includes the use of atropine, levodopa, and citicoline. In a PEDIG study of the use of atropine 1% solution on the fellow eye on weekends or once daily, both groups achieved comparable visual improvement.[17] In another PEDIG study of the use of atropine on weekends, improvement in VA was greater in children aged 3 to 7 years than in children aged 7 to 12 years (4.5-5.1 lines vs 1.5 lines).[18] Patching can achieve more rapid initial improvement, whereas atropine can achieve comparable outcome after 6 months,[19] with higher compliance and lower social stigma.[20] Adverse effects of atropine include photosensitivity, conjunctival irritation, dry mouth and skin, tachycardia, and fever. Atropine is not effective for myopia-induced amblyopia.

Levodopa-carbidopa combination therapy has been used to raise retinal dopamine level and exert neuromodulatory effect on visual development.[21] In children with severe amblyopia, patching plus high-dose levodopa resulted in better visual outcomes than patching alone.[22] However, in children aged 7 to 12 years who were refractory to patching, levodopa did not result in greater improvement in VA than placebo plus patching.[23] Levodopa may cause headache and nausea in some patients, but no serious adverse effect such as dyskinesia has been reported.

Citicoline increases the level of neurotransmitters (catecholamines, serotonin, and dopamine) and thus stimulates metabolism of the nigrostriatal dopaminergic system. Its cholinergic effect and neuroprotective effect protect integrity of neuronal cell membrane.[24] Citicoline alone is not more effective than patching, but citicoline plus patching can stabilize the improvement in VA obtained during treatment, whereas patching alone can result in a decrease in VA at 90 days after treatment.[25,26]

Bangerter filters are transparent filters placed in front of spectacles and are for those with mild amblyopia who are not responsive to spectacles alone. The occlusion effect of filters in different densities can change the VA of the fellow eye.[27] Bangerter filters achieve similar results to patching of 2 hours per day in patients with moderate amblyopia.[28]

Surgical treatment should be performed before amblyopia management in patients with structural disturbance along the visual axes (congenital cataract, vitreous hemorrhage, corneal opacities, and ptosis).

Perceptual learning is defined as any relatively permanent and consistent change in perception of stimulus array following practice or experience with this array by a variety of tasks such as vernier acuity, Gabor detection, and positional discrimination.[29] Perceptual learning aims to improve neural processing in visual cortex during the critical period. Perceptual learning can improve VA in the trained eye, but many patients remain to have a broader spatial frequency than normal.[30] However, perceptual learning is not a popular approach for treating amblyopia. The small sample size may overgeneralize the benefits of perceptual learning. More large-scale studies are warranted to determine the effectiveness of perceptual learning on treating amblyopia.

Binocular therapy

Amblyopia was considered to be a monocular visual deficit causing secondary binocular visual deficiency, and thus treatments are mainly monocular without binocular combination of stimuli.[31] However, there is growing evidence to support a binocular deficit secondary to active suppression of the amblyopic eye.[32] The cause of the binocular deficit in suprathreshold tasks in strabismic amblyopia is interocular suppression,[33] and the strength of which is associated with the degree of amblyopia.[34] By varying signal length of the attenuation of amblyopic eye, the binocular contrast summation in strabismic amblyopes can be normalized.[35] Thus, various binocular therapies are developed to improve both VA and binocular function.

Binocular contrast therapy aims to strengthen binocular visual function and reduce interocular suppression by providing high-contrast stimuli to amblyopic eye and low-contrast stimuli to the fellow eye.[36,37] The therapy involves playing videogames that tessellate high-contrast falling blocks to low-contrast stationary base to form a continuous row through goggles that split images between the eyes.[38-40] Other binocular games include the Ping-Pong game, Labyrinth game, and the Balloon game. Both eyes must be used to play the games as each eye does not see the full picture.

Interactive binocular treatment involves presenting dichoptic video or video games without contrast balancing to both eyes but with foreground elements to the amblyopic

Table. Binocular therapy for children with amblyopia

Study	No. of patients	Age, y	Binocular therapy	Outcome
Cleary et al,[42] 2009	12 (refractory to prior occlusion)	6.1-11.4	Interactive binocular treatment (I-BiT): 20 minutes watching video clip and 5 minutes playing interactive driving game for 11 weekly sessions	Sustained improvement in high-contrast visual acuity (VA) in 7 (58%) children and in low-contrast VA in 8 (67%) children
Knox et al,[39] 2012	14	8.5±2.6	Dichoptic perceptual learning by simple computer game, 5 sessions, each 1 hour over a week	VA improvement of the amblyopic eye from 0.51±0.27 to 0.42±0.28 logMAR. Improvement in stereofunction in 3 patients
Herbison et al,[43] 2013	10	5.4	I-BiT: 20 minutes watching video and 10 minutes playing interactive game once a week for 6 weeks	VA improvement in 9 patients
Li et al,[32] 2014	75	4-12	Sham games (n=25) or binocular games (n=50) with red-green anaglyphic glasses for 4 hours/week for 4 weeks	VA improvement from 0.47±0.03 to 0.39±0.03 logMAR in binocular group. No improvement in stereoacuity in both groups
Mansouri et al,[44] 2014	22 (refractory to patching and/or surgery)	5-73	Binocular training with dichoptic random dot kinematograms for 14.5 sessions in 4-6 weeks	VA improvement by 0.34 logMAR
Birch et al,[45] 2015	50	3-6.9	Sham iPad games (n=5) or binocular iPad games (n=45) for 4 hours/week for 4 weeks; 4 and 30 of children in the respective group received additional patching at a different time of day	VA improvement from 0.43±0.03 to 0.34±0.03 logMAR after dichoptic therapy
Webber et al,[46] 2016	20	8.5±1.3	Binocular treatment by dichoptic iPad games for 5 weeks	Improvement in fine motor skills especially in less severe amblyopia
Herbison et al,[47] 2016	75	4-8	I-BiT games using shutter glass technology (n=25), I-BiT DVD footage shown to the amblyopic eye and common background to both, modified shooter game with targets presented to amblyopic eye and background to both (n=25), and non–I-BiT games with both background and foreground presented to both eyes (n=25)	VA improvement by 0.07 logMAR at 6 weeks in three arms
Holmes et al,[52] 2016	385	5-13	16 weeks of a binocular iPad game for 1 hour a day or patching of the fellow eye for 2 hours a day	VA improvement in both groups; primary non-inferiority analysis yielded indeterminate results
Kelly et al,[48] 2016	28	4.6-9.5	Binocular game (n=14) or patching (n=14)	Greater stereoacuity and VA improvement in binocular game than patching (0.15 vs 0.07 logMAR)
Bossi et al,[49] 2017	22	3-11	Balanced binocular viewing therapy: viewing dichoptic movies and gameplay for maximum of 8 and 24 weeks, respectively	VA improvement by 0.27 logMAR after binocular therapy
Singh et al,[50] 2017	68	6-14	Video game for 1 hour/day plus occlusion therapy for 6 hours/day or occlusion alone for 6 hours/day	Greater VA improvement in video game plus occlusion therapy than occlusion alone (0.61±0.12 to 0.40±0.15 vs 0.65±0.09 to 0.48±0.10 logMAR)
Gao et al,[53] 2018	115 (89 had prior occlusion)	7-12, 13-17, ≥18	Case: playing falling-blocks video games with dichotic contrast at home on an iPod Touch for 1 hour/day for 6 weeks. Control: playing placebo video game with identical images to both eyes.	Improvement in visual outcomes was not significantly more in binocular therapy than placebo video game
Manh et al,[54] 2018	100	13-16	Binocular iPad game 1 hour/day or patching of the fellow eye for 2 hour/day for 16 weeks	Binocular therapy was not superior to patching in VA improvement of the amblyopia eye
Rajavi et al,[55] 2019	40	3-10	I-BiT games or patching with placebo video games for 1 month	Both groups achieved similar best-corrected VA improvement
Roy et al,[51] 2019	55	5-15	Dichoptic video game for 2 hours/day or occlusion therapy of 6 hours/day	Improvement in best-corrected VA from 0.70 to 0.49 logMAR in binocular group and from 0.73 to 0.52 logMAR in occlusion group. Improvement in near vision and contrast sensitivity in both groups. Significant improvement in near stereoacuity in binocular group only
Yao et al,[56] 2020	103	3-13	Binocular video game 40 minutes/day, patching 2-6 hours/day, or a combination of patching while playing video games on glasses for 3 months	Improvement in VA of the amblyopia eye and binocularity was less effective in binocular therapy than patching. No superiority in stereoacuity improvement in binocular therapy
Gao et al,[57] 2021	105	7-17	Active treatment or placebo videogame 1-2 hours/day for 6 weeks on iPod Touch device	Younger age groups showed lower adherence to binocular treatment

eye only. The key element is only seen by the amblyopic eye, but both eyes must be used to watch/play the video game. For instance, the non-amblyopic eye receives peripheral stimuli and the amblyopic eye receives moving stimuli. Images can even be moved towards different directions to correct the angle of strabismus.[41]

The **Table** summarizes outcomes of various binocular therapies for children with amblyopia.[32,39,42-57] Most binocular therapies involve home-based dichoptic video games or movie watching for several hours a day over few months. Binocular therapy can replace occlusion therapy or can be an adjunct when the patient is refractory to conventional amblyopic treatment. In some studies, binocular therapy is effective in improving VA in amblyopic children and is superior to the conventional occlusion therapy.[32,39,42-51] In other studies, binocular therapy is not superior to patching.[52-56] Acceptability to binocular therapy is generally high among children with amblyopia,[47] compared with patching that has cosmetic concern on self-esteem. No major complication or risk is caused by binocular therapy. Nonetheless, compliance varies in different localities with different cultural and social backgrounds. Low compliance to binocular video game playing or watching may affect the outcome. Some studies are limited by the short treatment duration, short follow-up period, and small sample size; more comprehensive randomized controlled trials are warranted.

Optimal treatment duration and dosage as well as screening and surveillance

Amblyopia treatment is more effective in the first 6 months of treatment. For refractive correction, improvement is maximal in the first 400 hours of patching.[58] The Monitored Occlusion Treatment of Amblyopia Study attempted to determine the dose-response relationship of patching, but there was difficulty in measuring the actual dose received and in ensuring compliance to the prescribed therapy.[59] Statistical modeling has been used to determine the personalized dosage of treatment for maximal visual improvement.[60] Screening amblyopia at young age enables timely management within the critical period. However, screening too early may result in high false-positive results, whereas delayed screening may result in poor visual outcome. Surveillance is required to detect recurrence of amblyopia within 52 weeks of treatment cessation. About 25% of patients have recurrence within the first year of treatment cessation, especially when treatment is stopped abruptly rather than gradually.[16] Improvement in VA can deteriorate in long run. Thus, follow-up is important, especially in those with poor initial VA. There is no consensus on the optimal treatment duration, timing of initiation, dosage, screening, and surveillance of amblyopia. Further studies are warranted.

Conclusion

Amblyopia is a reversible neurodevelopmental disorder but can cause vision loss if untreated, especially within critical period of visual neuroplasticity. Apart from conventional treatment modalities (refractive correction, occlusion therapy, medication, surgery, and perceptual learning), the more advanced binocular therapy is increasingly popular. Binocular therapy can improve both VA and stereoacuity, but whether it is superior to occlusion therapy remains controversial. Future studies to determine the optimal treatment duration, timing of initiation, dosage, and when to step up treatment when other treatments become refractory 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 an editor of the journal, JCSY was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

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

References

1. *Sen S, Singh P, Saxena R. Management of amblyopia in pediatric patients: current insights. Eye (Lond) 2022;36:44-56.* Crossref
2. *Wallace DK, Repka MX, Lee KA, et al. Amblyopia Preferred Practice Pattern®. Ophthalmology 2018;125:P105-P142.* Crossref
3. *Williams C, Northstone K, Howard M, Harvey I, Harrad RA, Sparrow JM. Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. Br J Ophthalmol 2008;92:959-64.* Crossref
4. *Wong AMF. New concepts concerning the neural mechanisms of amblyopia and their clinical implications.*

Can J Ophthalmol 2012;47:399-409. Crossref
5. *Espinosa JS, Stryker MP. Development and plasticity of the primary visual cortex. Neuron 2012;75:230-49.* Crossref
6. *Scheiman MM, Hertle RW, Beck RW, et al. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. Arch Ophthalmol 2005;123:437-47.* Crossref
7. *Davis AR, Sloper JJ, Neveu MM, Hogg CR, Morgan MJ, Holder GE. Differential changes of magnocellular and parvocellular visual function in early- and late-onset strabismic amblyopia. Invest Ophthalmol Vis Sci 2006;47:4836-41.* Crossref
8. *Levi DM. Crowding—an essential bottleneck for object recognition: a mini-review. Vision Res 2008;48:635-54.* Crossref
9. *Webber AL. The functional impact of amblyopia. Clin Exp Optom 2021;101:443-50.* Crossref
10. *Webber AL, Wood JM, Gole GA, Brown B. Effect of amblyopia on self-esteem in children. Optom Vis Sci 2008;85:1074-81.* Crossref
11. *Wu C, Hunter DG. Amblyopia: diagnostic and therapeutic options. Am J Ophthalmol 2006;141:175-84.* Crossref
12. *Cotter SA. Treatment of anisometropic amblyopia in children with refractive correction. Ophthalmology 2006;113:895-903.* Crossref
13. *Tang EWH, Li BCY, Yeung IYL, Li KKW. Occlusion therapy in amblyopia: an experience from Hong Kong. Hong Kong Med J 2014;20:32-6.* Crossref
14. *Repka MX, Beck RW, Holmes JM, et al. A randomized trial of patching regimens for treatment of moderate amblyopia in children. Arch Ophthalmol 2003;121:603-11.* Crossref
15. *Scheiman MM, Hertle RW, Kraker RT, et al. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. Arch Ophthalmol 2008;126:1634-42.* Crossref
16. *Holmes JM, Beck RW, Kraker RT, et al. Risk of amblyopia recurrence after cessation of treatment. J AAPOS 2004;8:420-8.* Crossref
17. *Repka MX, Cotter SA, Beck RW, et al. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. Ophthalmology 2004;111:2076-85.* Crossref
18. *Repka MX, Kraker RT, Beck RW, et al. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. J AAPOS 2009;13:258-63.* Crossref
19. *Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. Arch Ophthalmol 2002;120:268-78.* Crossref
20. *Holmes JM, Beck RW, Kraker RT, et al. Impact of patching and atropine treatment on the child and family in the amblyopia treatment study. Arch Ophthalmol 2003;121:1625-32.* Crossref
21. *Luvone PM, Tigges M, Fernandes A, Tigges J. Dopamine synthesis and metabolism in rhesus monkey retina: development, aging, and the effects of monocular visual deprivation. Vis Neurosci 1989;2:465-71.* Crossref
22. *Sofi IA, Gupta SK, Bharti A, Tantry TG. Efficiency of the occlusion therapy with and without levodopa-carbidopa in amblyopic children: a tertiary care centre experience. Int J Health Sci (Qassim) 2016;10:249-57.* Crossref
23. *Pediatric Eye Disease Investigator Group; Repka MX, Kraker RT, et al. A randomized trial of levodopa as treatment for residual amblyopia in older children. Ophthalmology 2015;122:874-81.* Crossref
24. *Kapatos G. The neurobiology of tetrahydrobiopterin biosynthesis: a model for regulation of GTP cyclohydrolase I gene transcription within nigrostriatal dopamine neurons. IUBMB Life 2013;65:323-33.* Crossref
25. *Fresina M, Dickmann A, Salerni A, De Gregorio F, Campos EC. Effect of oral CDP-choline on visual function in young amblyopic patients. Graefes Arch Clin Exp Ophthalmol 2008;246:143-50.* Crossref
26. *Pawar PV, Mumbare SS, Patil MS, Ramakrishnan S. Effectiveness of the addition of citicoline to patching in the treatment of amblyopia around visual maturity: a randomized controlled trial. Indian J Ophthalmol 2014;62:124-9.* Crossref
27. *Bangerter A. Occlusion in pleoptics and orthoptics [in German]. Klin Monbl Augenheilkd Augenarztl Fortbild 1960;136:305-31.*
28. *Pediatric Eye Disease Investigator Group Writing Committee; Rutstein RP, Quinn GE, et al. A randomized trial comparing Bangerter filters and patching for the treatment of moderate amblyopia in children. Ophthalmology 2010;117:998-1004.e6.* Crossref
29. *Gibson EJ. Perceptual learning. Annu Rev Psychol 1963;14:29-56.* Crossref
30. *Levi DM, Li RW. Perceptual learning as a potential treatment for amblyopia: a mini-review. Vision Res 2009;49:2535-49.* Crossref
31. *Hess RF, Mansouri B, Thompson B. Restoration of binocular vision in amblyopia. Strabismus 2011;19:110-8.* Crossref
32. *Li SL, Jost RM, Morale SE, et al. A binocular iPad treatment for amblyopic children. Eye (Lond) 2014;28:1246-53.* Crossref
33. *Mansouri B, Thompson B, Hess RF. Measurement of suprathreshold binocular interactions in amblyopia. Vision Res 2008;48:2775-84.* Crossref
34. *Li J, Hess RF, Chan LYL, et al. Quantitative measurement of interocular suppression in anisometropic amblyopia: a case-control study. Ophthalmology 2013;120:1672-80.* Crossref
35. *Baker DH, Meese TS, Mansouri B, Hess RF. Binocular summation of contrast remains intact in strabismic amblyopia. Invest Ophthalmol Vis Sci 2007;48:5332-8.* Crossref
36. *Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. Restor Neurol Neurosci 2010;28:793-802.* Crossref
37. *Hess RF, Thompson B. Amblyopia and the binocular approach to its therapy. Vision Res 2015;114:4-16.* Crossref
38. *To L, Thompson B, Blum JR, Maehara G, Hess RF, Cooperstock JR. A game platform for treatment of amblyopia. IEEE Trans Neural Syst Rehabil Eng 2011;19:280-9.* Crossref
39. *Knox PJ, Simmers AJ, Gray LS, Cleary M. An exploratory study: prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. Invest Ophthalmol Vis Sci 2012;53:817-24.* Crossref
40. *Black JM, Hess RF, Cooperstock JR, To L, Thompson B. The measurement and treatment of suppression in amblyopia. J Vis Exp 2012;70:e3927.* Crossref
41. *Foss AJ, Gregson RM, MacKeith D, et al. Evaluation and development of a novel binocular treatment (I-BiT) system using video clips and interactive games to improve vision in children with amblyopia ('lazy eye'): study protocol for a randomised controlled trial. Trials 2013;14:145.* Crossref
42. *Cleary M, Moody AD, Buchanan A, Stewart H, Dutton GN. Assessment of a computer-based treatment for older amblyopes: the Glasgow Pilot Study. Eye (Lond) 2009;23:124-31.* Crossref
43. *Herbison N, Cobb S, Gregson R, et al. Interactive binocular treatment (I-BiT) for amblyopia: results of a pilot study of 3D shutter glasses system. Eye (Lond) 2013;27:1077-83.* Crossref

44. *Mansouri B, Singh P, Globa A, Pearson P. Binocular training reduces amblyopic visual acuity impairment. Strabismus 2014;22:1-6.* Crossref
45. *Birch EE, Li SL, Jost RM, et al. Binocular iPad treatment for amblyopia in preschool children. J AAPOS 2015;19:6-11.* Crossref
46. *Webber AL, Wood JM, Thompson B. Fine motor skills of children with amblyopia improve following binocular treatment. Invest Ophthalmol Vis Sci 2016;57:4713-20.* Crossref
47. *Herbison N, Mackeith D, Vivian A, et al. Randomised controlled trial of video clips and interactive games to improve vision in children with amblyopia using the I-BiT system. Br J Ophthalmol 2016;100:1511-6.* Crossref
48. *Kelly KR, Jost RM, Dao L, Beauchamp CL, Leffler JN, Birch EE. Binocular iPad game vs patching for treatment of amblyopia in children: a randomized clinical trial. JAMA Ophthalmol 2016;134:1402-8.* Crossref
49. *Bossi M, Tailor VK, Anderson EJ, et al. Binocular therapy for childhood amblyopia improves vision without breaking interocular suppression. Invest Ophthalmol Vis Sci 2017;58:3031-43.* Crossref
50. *Singh A, Sharma P, Saxena R. Evaluation of the role of monocular video game play as an adjuvant to occlusion therapy in the management of anisometropic amblyopia. J Pediatr Ophthalmol Strabismus 2017;54:244-9.* Crossref
51. *Roy S, Saxena R, Sharma P, Phuljhele S. Comparative evaluation of binocular visual stimulation versus occlusion therapy in children with anisometropic amblyopia. J AAPOS 2019;23:e51.* Crossref
52. *Holmes JM, Manh VM, Lazar EL, et al. Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia: a randomized clinical trial. JAMA Ophthalmol 2016;134:1391-400.* Crossref
53. *Gao TY, Guo CX, Babu RJ, et al. Effectiveness of a binocular video game vs placebo video game for improving visual functions in older children, teenagers, and adults with amblyopia: a randomized clinical trial. JAMA Ophthalmol 2018;136:172-81.* Crossref
54. *Manh VM, Holmes JM, Lazar EL, et al. A randomized trial of a binocular iPad game versus part-time patching in children aged 13 to 16 years with amblyopia. Am J Ophthalmol 2018;186:104-15.* Crossref
55. *Rajavi Z, Sabbaghi H, Amini Sharifi E, Behradfar N, Kheiri B. Comparison between patching and interactive binocular treatment in amblyopia: a randomized clinical trial. J Curr Ophthalmol 2019;31:426-31.* Crossref
56. *Yao J, Moon HW, Qu X. Binocular game versus part-time patching for treatment of anisometropic amblyopia in Chinese children: a randomised clinical trial. Br J Ophthalmol 2020;104:369-75.* Crossref
57. *Gao TY, Black JM, Babu RJ, et al. Adherence to home-based videogame treatment for amblyopia in children and adults. Clin Exp Optom 2021;104:773-9.* Crossref
58. *Cleary M. Efficacy of occlusion for strabismic amblyopia: can an optimal duration be identified? Br J Ophthalmol 2000;84:572-8.* Crossref
59. *Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Invest Ophthalmol Vis Sci 2004;45:3048-54.* Crossref
60. *Wallace MP, Stewart CE, Moseley MJ, Stephens DA, Fielder AR; MOTAS and ROTAS Cooperatives. Treatment of amblyopia using personalized dosing strategies: statistical modelling and clinical implementation. Strabismus 2016;24:161-8.* Crossref

Expert opinions on benefit-risk profile and clinical use of brolucizumab

Nicholas Fung[1], *FHKAM, FCOphHK, MRCS, MBChB; Danny Ng*[2], *FRCSEd, FCOphthHK; Ian Wong*[3], *FRCOphth, MD; Raymond Wong*[4], *FHKAM, MRCSEd; Pui Pui Yip*[5], *FHKAM, FCOphHK; Alvin KH Kwok*[3], *MD, PhD, FHKAM, FRCOphth, FCOphth, FCSHK, FRCSEd, PDip Epidemiology and Biostatistics, MBBS; Wai Ching Lam*[1], *MD, FRCSC; Timothy YY Lai*[2], *MD, FRCOphth; Ramin Khoramnia*[6], *MD, FEBO*

[1]*Department of Ophthalmology, The University of Hong Kong, Hong Kong SAR, China*
[2]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China*
[3]*Hong Kong Sanatorium and Hospital, Hong Kong SAR, China*
[4]*C-MER Dennis Lam and Partners Eye Center, Hong Kong SAR, China*
[5]*Champion Eye and Refractive Surgery Centre, Hong Kong SAR, China*
[6]*University Eye Clinic, University Hospital Heidelberg, Germany*

Correspondence and reprint requests:
Dr Timothy YY Lai, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China. Email: tyylai@cuhk.edu.hk

Abstract

Brolucizumab is a next-generation anti–vascular endothelial growth factor (VEGF) agent for the treatment of neovascular age-related macular degeneration. It is highly potent and thus appropriate for those unresponsive to other anti-VEGF agents and those undertreated owing to the low adherence or the heavy burden of repeated injections. An expert panel of 10 retina specialists from Hong Kong and Germany convened in February 2021 to discuss the benefit-risk profile and clinical use of brolucizumab. Evidence suggests that brolucizumab provides comparable visual outcomes to aflibercept at a more relaxed injection schedule. Brolucizumab is superior to aflibercept in resolving intraretinal and subretinal fluids and decreasing disease activity. Brolucizumab is suitable for patients unresponsive to other anti-VEGF agents, especially for those with persistent intraretinal and subretinal fluids or disease activity. Injection intervals of brolucizumab can be extended to 8 to 12 weeks. However, brolucizumab has higher risk of adverse events such as intraocular inflammation, retinal vasculitis, and retinal occlusion, compared with aflibercept. Thus, regular monitoring for signs of intraocular inflammation and prompt management are important before and during treatment.

Key words: Brolucizumab; Injections, intraocular; Macular degeneration; Vascular endothelial growth factor A

Introduction

Brolucizumab is a next-generation drug for neovascular age-related macular degeneration (nAMD).[1] The general treatment goals are to maintain and improve visual acuity (VA), reduce vascular leakage, and induce regression of neovascularization.[2] Intravitreal injections of anti–vascular endothelial growth factor (anti-VEGF) agents (aflibercept, bevacizumab, ranibizumab, and brolucizumab) to inhibit abnormal blood vessel development are the most effective approach (**Table 1**).[2-5] Anti-VEGF agents are effective as long as strict and frequent regimens are followed, but in clinical settings undertreatment is the norm.[6-10] Over 70% of patients are undertreated during their first year,[11] and about 60% of patients are non-adherent after 2 years.[12] The low adherence may be partly due to the burden of repeated injections. Anti-VEGF agents that can be administered at less frequent intervals are needed.[13]

Brolucizumab (Beovu, Novartis, Basel, Switzerland)[14] is a single-chain antibody fragment comprising a scaffold attached to an anti-VEGF-A antibody that inhibits all isoforms of VEGF-A at a 2:1 ratio. It binds to VEGF-A isoforms and prevents their interaction with receptors VEGFR1 and VEGFR2, thereby suppressing endothelial cell proliferation, neovascularization, and vascular permeability.[15-20] The small molecular size of brolucizumab enables large molar dosages per injection, better penetration into ocular tissue, and greater fluid resolution.[1,17,18] These benefits result in longer injection intervals (up to every 12 weeks).[14] Furthermore, brolucizumab is easy to tolerate, as single-chain antibody fragments generally have high

stability and solubility *in vivo*.[15] Trials in animal models suggest rapid systemic clearance and low exposure.[17,18,21]

In February 2021, an expert panel comprising 10 retina specialists from public, private, and academic institutions convened to discuss evidence on the use of brolucizumab in clinical practice in Hong Kong. This study summarized the expert opinions on the benefit-risk profile and clinical use of brolucizumab.

Benefit-risk profile

In the HAWK and HARRIER phase III trials, treatment-naïve patients aged >50 years were randomly assigned to receive brolucizumab or aflibercept (HAWK: 3 mg brolucizumab [n=358], 6 mg brolucizumab [n=360], 2 mg aflibercept [n=360]; HARRIER: 6 mg brolucizumab [n=370], 2 mg aflibercept [n=369]) and were followed up for 96 weeks.[22,23] Both trials began with a loading phase of injections at weeks 0, 4, and 8, followed by 8 weeks with no injection. The 16-week loading phase was identical between arms. Then, brolucizumab was administered every 12 weeks (or every 8 weeks in patients with disease activity), whereas aflibercept was administered every 8 weeks. Patients were assessed at weeks 16, 20, 32, and 44 for best-corrected visual acuity (BCVA), disease activity, intraretinal fluid (IRF), subretinal fluid (SRF), sub-retinal pigment epithelium (sub-RPE) fluid, and central subfield thickness (CST). Patients in the HARRIER trial were additionally assessed at weeks 28 and 40. Non-inferiority of brolucizumab against aflibercept was determined by the BCVA change from baseline to week 48, whereas safety was determined by the incidence of adverse events.

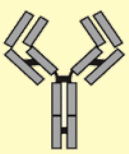
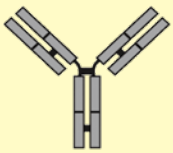
Benefits

In the HAWK and HARRIER trials, brolucizumab achieved comparable BCVA results to aflibercept despite having longer intervals (**Table 2**).[22,23] Brolucizumab was superior to aflibercept in controlling disease activity and IRF/SRF. Compared with 2 mg aflibercept, 6 mg brolucizumab resulted in about 36% less disease activity at 16 weeks after first dose, and 30% to 50% less IRF/SRF and sub-RPE fluid. Brolucizumab resulted in stronger and more consistent reduction in CST than aflibercept, with better improvement in the morphology of the macula.

In a study that pooled data from the HAWK and HARRIER trials and presented at the European Society of Retina Specialists 2020 Congress, brolucizumab resulted in quicker resolution of IRF/SRF than aflibercept, with lower incidence of persistent IRF/SRF over the first 12 weeks (12.5% vs 20.4%).[24] In patients with early persistent IRF/SRF, VA improvement was greater after brolucizumab treatment, with 8%, 48%, and 59% more patients achieving BCVA gain of ≥15 letters at 16, 48, and 96 weeks, respectively.

Retrospective reviews and case studies confirm brolucizumab's effectiveness at suppressing disease activity (in terms of reduction in CST, fluid compartments, and large pigment epithelial detachments, and improvement in VA outcomes) in the short-term, especially for patients unresponsive to other anti-VEGF agents.[25-30] In the BRAILLE chart review of 20 treatment-naïve patients and 74 recalcitrant patients who received a mean of 1.36 injections of brolucizumab and were followed up for 5 to 30 weeks, those recalcitrant patients who switched to brolucizumab had significant improvement in BCVA from 0.91 logMAR at baseline to 0.73 logMAR at final checkup, whereas all patients had an average reduction in CST of >100 μm, and >80% of treated eyes showed reduction or complete resolution of SRF, IRF, and pigment epithelial detachments.[27] In the REBA study of 23 treatment-naïve patients and 55 recalcitrant patients who switched to brolucizumab and were followed up for >9 months, >70% of treatment-naïve eyes had complete resolution of IRF/SRF by the end of the loading phase, whereas all recalcitrant patients who switched to brolucizumab had complete resolution of disease activity by their third brolucizumab injection.[29] Both groups of patients showed a gain of an average of 10 ETDRS (Early Treatment Diabetic Retinopathy Study) letters and a reduction of CST of >150 μm.

Table 1. Comparison of anti–vascular endothelial growth factor agents[16]

	Aflibercept	Bevacizumab	Ranibizumab	Brolucizumab
Molecular structure	VEGFR1/2-Fc fusion protein 	IgGI antibody 	Antigen-binding fragment 	Single-chain antibody fragment 
Molecular weight, kDa	97-115	~149	~48	26
Clinical dose, mg	2.00	1.25	0.30-0.50	6.00
Equivalent molar dose (to aflibercept)	1.0	0.4-0.5	0.5-0.6	11.2-13.3
Injection interval	Every 8 weeks	Every 4 weeks	Every 4 weeks	Every 8 to 12 weeks

Risks

In the HAWK and HARRIER trials, over half of the patients had adverse events such as conjunctival hemorrhage, cataracts, vitreous floaters, and VA reduction, and the rate was comparable in the brolucizumab and aflibercept arms (**Table 3**).[22,23] In the pooled brolucizumab group, nine patients had suspected endophthalmitis.[1] Of them, three were negative and two were positive for *Staphylococcus* or *Streptococcus mitis*, and the others were not tested or uninterpretable.

Brolucizumab is associated with greater risks of intraocular inflammation (IOI) than aflibercept.[22,23] According to an independent safety review committee, brolucizumab carries risks of severe vision loss secondary to retinal vasculitis or retinal artery/vascular occlusion, which tend to occur in the presence of IOI.[31,32] Thus, the consensus is to discontinue brolucizumab in any case of IOI.[31-34] Adverse events tend to develop within the first three injections of brolucizumab and after 3 weeks of the preceding injection, but the time from first injection to first IOI-related adverse event can

Table 2. Clinical outcomes of the HAWK and HARRIER phase III clinical trials at 16, 48, and 96 weeks[22,23]

	HAWK trial			HARRIER trial		
	6 mg brolucizumab (n=360)*	2 mg aflibercept (n=360)*	p Value	6 mg brolucizumab (n=370)*	2 mg aflibercept (n=369)*	p Value
Change in best-corrected visual acuity, No. of ETDRS letters						
Week 48	6.6±0.71	6.8±0.71	<0.001	6.9±0.61	7.6±0.61	<0.001
Week 96	5.9±0.78	5.3±0.78	-	6.1±0.73	6.6±0.73	-
Disease activity						
Week 16	24.0	34.5	0.001	22.7	32.2	0.001
Presentation of intraretinal/subretinal fluid						
Week 16	33.9	52.2	0.001	29.4	45.1	<0.001
Week 48	31.2	44.6	<0.001	25.8	43.9	<0.001
Week 96	24.0	37.0	-	24.0	39.0	-
Presentation of sub-retinal pigment epithelium fluid						
Week 48	13.5	21.6	0.004	12.9	22.0	<0.001
Week 96	11.0	15.0	0.121	17.0	22.0	0.037
Change in central subfield thickness, μm						
Week 16	-161.4	-133.6	<0.001	-174.4	-134.2	<0.001
Week 48	-172.8	-143.7	0.001	-193.8	-143.9	<0.001
Week 96	-174.8	-148.7	0.012	-197.7	-155.1	<0.001

** Data are presented as least squared mean±standard error, least squared mean, or % of eyes*

Table 3. Incidences of adverse events reported by the HAWK and HARRIER phase III clinical trials and an independent safety review committee[22,23,31,32]

Adverse event	HAWK trial		HARRIER trial		Safety review committee	
	6 mg brolucizumab (n=360)	2 mg aflibercept (n=360)	6 mg brolucizumab (n=370)	2 mg aflibercept (n=369)	Brolucizumab (n=1088)	Aflibercept (n=729)
	No. (%) of patients or % of patients					
Ocular adverse event at 96 weeks	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)	-	-
Serious ocular adverse event at 96 weeks	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)	-	-
Intraocular inflammation	17 (4.7)	2 (0.6)	3 (0.8)	4 (1.1)	50 (4.6)	8 (1.1)
Retinal vasculitis	-	-	-	-	36 (3.3)	-
Retinal artery and vascular occlusion	4 (1.1)	0 (0.0)	2 (0.5)	1 (0.3)	23 (2.1)	-
Endophthalmitis	4 (1.1)	0 (0.0)	1 (0.3)	1 (0.3)	9 (<0.1)	-
Loss of ≥15 ETDRS letters at 96 weeks	8.1	7.4	7.1	7.5	7.4 (at 48 weeks)	7.7 (at 48 weeks)

be up to 18 months.[35] The mechanism of brolucizumab-related adverse events may be associated with a delayed hypersensitivity response, impurities in the serum, or excessive VEGF inhibition.[36,37]

Intraocular inflammation

The safety review committee identified 50 definite or probable cases of IOI in all brolucizumab-treated eyes (n=1088) in the HAWK and HARRIER trials, compared with eight cases in the aflibercept arms (**Table 3**).[31] IOI tends to occur early in treatment, with about 50% and 80% occurring within 3 and 12 months, respectively; earlier occurrence is associated with greater risk of vision loss.[1,31,32,35] According to medical claim data in the IRIS Registry and Komodo study, the incidence of IOI within 6 months of the first brolucizumab injection was 2.4%, with prior IOI or retinal occlusion being a risk factor.[38] Most IOI cases in the HAWK and HARRIER trials were mild to moderate and were resolved without sequelae.[1,35] Most severe IOI cases did not result in diminished VA outcomes; of 49 patients with severe IOI, only 14 had loss of BCVA, whereas 23 had improved and 12 had stable BCVA.[1]

IOI may precede retinal vasculitis or retinal occlusion by 16 to 171 days.[35] Uveitis, iritis, vitritis, and iridocyclitis are the most common initial presentations of IOI before retinal vasculitis or retinal occlusion.[35] Signs of IOI include inflammatory cells in anterior and/or posterior segments, vitreous cells or opacities, non-granulomatous keratic precipitates, conjunctival injection, Descemet's membrane, and corneal edema.[35]

The incidence of IOI appeared to be higher in Japanese patients.[39,40] According to the Japan AMD Research Consortium study of 127 eyes treated with brolucizumab, the rate of IOI during the first 6 months was notably high at 9% to 10%,[39] which was nevertheless lower than the 13% reported by the safety review committee for Japanese patients in the HAWK trial. In a post-hoc analysis of Japanese patients with polypoidal choroidal vasculopathy in the HAWK trial, the rate of IOI was higher in brolucizumab users than aflibercept users (15% vs 0%), but the sample size was too small to perform post-hoc statistical analysis.[40] Ophthalmologists should be aware that Japanese populations may be at greater risk of IOI, but the evidence remains inconclusive.

Retinal vasculitis, retinal occlusion, and vision loss

Of the 50 eyes with IOI identified by the safety review committee, 36 involved retinal vasculitis and 23 involved retinal vasculitis and retinal occlusion (**Table 3**).[31,32] Nonetheless, the overall risk of moderate or severe vision loss was <1%, which is similar to that for aflibercept. For all vision loss cases, brolucizumab was associated with a 7.4% risk of vision loss within 2 years, compared with 7.7% for aflibercept. Most vision loss cases were caused by the degenerative nature of nAMD and were not drug-related.[1]

Records for adverse events associated with brolucizumab are submitted by practitioners worldwide to the website: https://www.brolucizumab.info/. From October 2019 to September 2021, for every 10,000 injections, there were 5.4 cases of retinal vasculitis, 3.3 cases of retinal occlusion, and 7.0 cases of both (15.7 cases overall), of them 4.9 cases were severe vision loss.

Recommendations

Brolucizumab is comparable with aflibercept in terms of VA outcomes but has a more relaxed treatment schedule that may facilitate adherence. Brolucizumab achieves better outcome in terms of resolving fluids, controlling disease activity, and improving macula morphology. Brolucizumab-associated adverse events are rare. Nevertheless, patients should be regularly assessed for IOI signs after administering brolucizumab, as onset may be nonspecific and may develop weeks after injection. Early diagnosis is important for timely intervention, treatment, and monitoring. Brolucizumab is contraindicated when IOI is suspected.[35] Measures to reduce risk are the same as those for other anti-VEGF agents. It is important to avoid injecting any anti-VEGF agent into an inflamed eye. Ophthalmologists should arrange the times of assessment and injection close to each other and follow up on any reports of suspicious symptoms. A management plan for the clinical use of brolucizumab is shown in the **Figure**.

Patient selection

Brolucizumab can be used in both treatment-naive patients and patients with ongoing anti-VEGF therapy. Currently, brolucizumab is mostly used in patients with ongoing anti-VEGF therapy. It is advisable to keep using the existing agents if effective; there is no need to switch to brolucizumab if the injection schedule can be extended to at least every 8 weeks. Brolucizumab should be avoided in patients with a history of IOI or retinal occlusion in the preceding 12 months. Brolucizumab can be considered in treatment-naïve patients with persistent SRF and sub-RPE fluid (eg, polypoidal choroidal vasculopathy). Brolucizumab can also be considered in patients with difficulty controlling disease activity or improving macula morphology and in patients struggling to extend treatment interval beyond 4 to 6 weeks.[22,23] Brolucizumab is appropriate in patients unresponsive to other anti-VEGF agents including those with polypoidal choroidal vasculopathy or pigment epithelial detachments.[25,40] Guidelines are helpful to avoid selecting patients at risk of adverse events and to provide treatment approaches.[33,34] Screening patients for IOI risks may help alleviate concerns.

Monitoring

Pre-existing IOI and signs of inflammation should be ruled out with a dilated-pupil fundus examination before the loading injection. When switching to brolucizumab, patients should be closely monitored for any manifestation of drug-associated IOI during the initial 6 months and even 18 months, as IOI can develop up to 18 months from the first injection.[35] Complete ophthalmic examination with

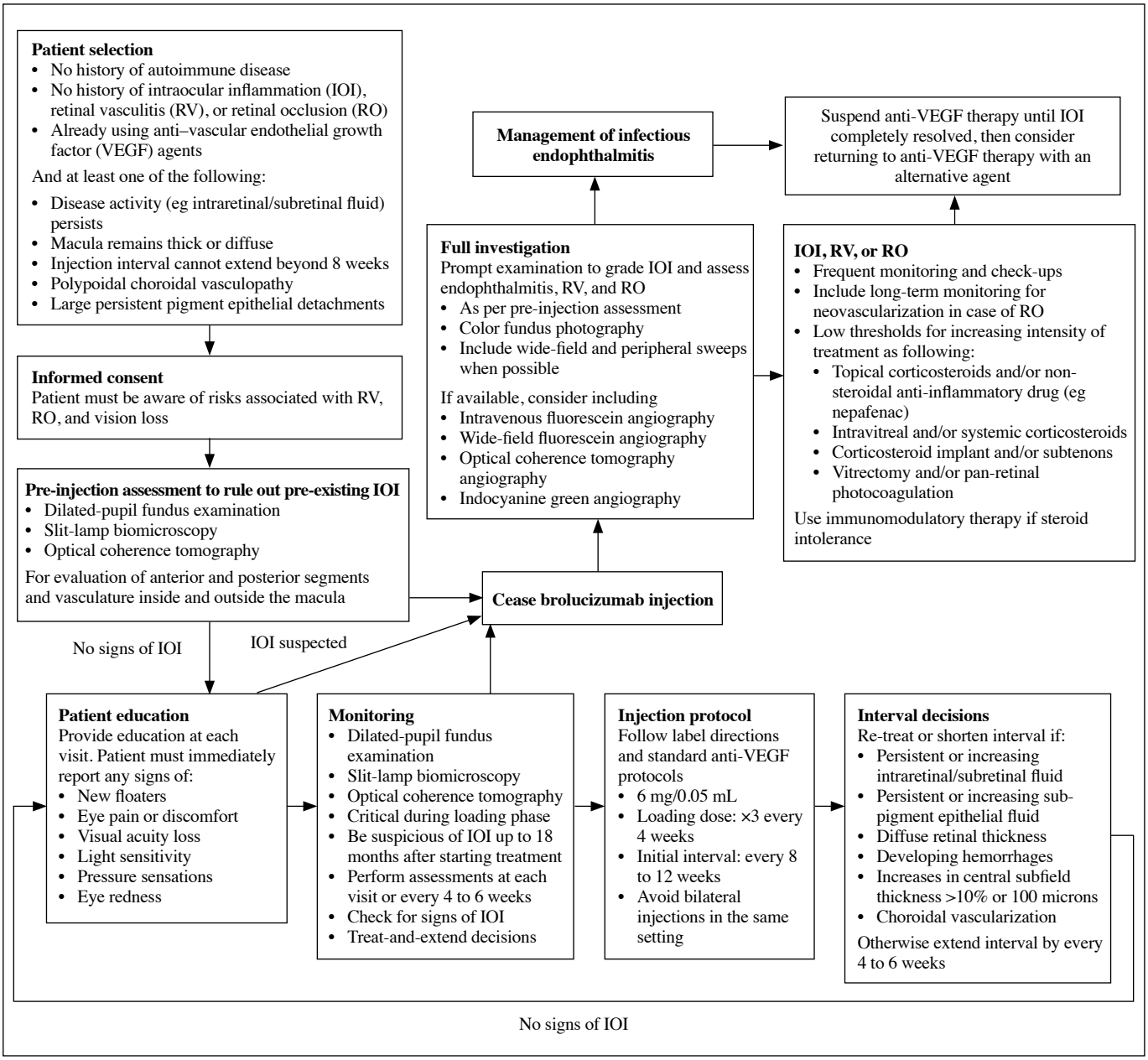


Figure. Proposed management plan for clinical use of brolucizumab[33-35]

slit-lamp biomicroscopy, dilated fundoscopy, and optical coherence tomography should be performed at every visit before injection or at regular intervals of 4 to 6 weeks.[35] Signs of IOI, retinal vasculitis, and retinal occlusion at any stage should be managed with prompt and intensive treatment.[33,34] Patients must be educated about symptoms such as floaters, pain, pressure sensations, light sensitivity, and decreased VA to be reported to physicians.[34] Education must be provided at each visit, and immediate reporting must be stressed. Any reports of suspicious symptoms should be examined immediately, and brolucizumab should be halted at any sign of IOI. Optical coherence tomography can be used to monitor disease activity and inform decisions on injection intervals. An injection interval of 12 to 16 weeks should be targeted, although stability at every 8 weeks is acceptable. Decision to extend interval should be supported by the absence of signs of recurring disease activity.

Diagnosis and treatment of intraocular inflammation, retinal vasculitis, and retinal occlusion

Guidelines for diagnosis and treatment of adverse events have been reported.[33,34] Differential diagnosis of infectious endophthalmitis must be ruled out, as it requires a different treatment course (intravitreal antibiotics). Infectious endophthalmitis typically has a more acute onset of symptoms such as hypopyon arising within 1 week of injection, compared with subacute symptoms that tend to arise about 3 weeks after injection and lack hypopyon. Patients should

be evaluated for underlying systemic or infectious diseases that may cause IOI such as giant cell arteritis and collagen vascular diseases. Optical coherence tomography and wide-field or peripheral-field fluorescein angiography should be used for diagnosing. The diagnosis of retinal vasculitis should be confirmed by evaluation of vessel involvement. Treatment regimen should follow a gradient of intensive corticosteroids based on the severity of IOI and/or vascular involvement. Immunomodulating therapy, vitrectomy, and pan-retinal photocoagulation are alternative treatment options, especially for steroid-intolerant patients. If there is no vascular involvement and the IOI is mild, intensive topical corticosteroids can be used. Close monitoring and gradual tapering of dosage can be considered if conditions improve. Patients who fail to respond or worsen should be offered systemic and/or intravitreal corticosteroids. For retinal vasculitis, retinal occlusion, and moderate-to-severe IOI, immediate systemic and intravitreal corticosteroids supplemented with topical corticosteroids should be used. Other adjunctive therapies include corticosteroid implants and/or subtenon steroid injections.

Conclusion

IRF and SRF are pathological features of nAMD, and their resolution is the key to achieve good BCVA outcomes and to extend treatment intervals. However, unresolved IRF/SRF and non-adherence to the treatment schedule may result in vision loss. Moreover, the high frequency of injections burdens healthcare providers and patients. Brolucizumab (6 mg) is effective to improve vision, resolve IRF/SRF, and extend treatment intervals to ≥12 weeks. Brolucizumab has a well-tolerated safety profile. Its rate of vision loss is comparable to that of aflibercept. A safe and effective management plan should involve proper patient selection, regular monitoring (especially in the first 18 months of therapy), and prompt intensive treatment of adverse events.

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 in partnerships with Alcon, Allergan, Bayer, Chengdu Kanghong Pharm, Novartis, and Roche, and has received honoraria and research grant from them. RW has received honoraria from Bayer, Novartis, and Roche. WCL has received research grant and honoraria from Alcon and Bayer and honoraria from Allergan and Novartis. TYYL has received honoraria and grant support from Allergan, Bayer, Boehringer Ingelheim, Chengdu Kanghong Biotech, Novartis, and Roche. RK has received grant and financial support from Alimera, Allergan, Bayer, Chengdu Kanghong, Novartis, and Roche. All other authors have received honoraria from Novartis. As editors of the journal, AKHK, WCL, and TYYL were not involved in the peer review process.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. However, honorariums were provided by Novartis Pharmaceuticals (Hong Kong) to panel experts in relation to this meeting. The funder had no role in study design or interpretation or in manuscript preparation other than providing fund for the medical writer.

Data availability

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

Acknowledgments

Medical writing assistance by Stephen Heap of MIMS (Hong Kong) was funded by Novartis Pharmaceuticals (Hong Kong) and complied with Good Publication Practice 3 ethical guidelines.

References

1. *Novartis Pharma AG. Core Submission Dossier PTJA09. Available from: https://www.eunethta.eu/wp-content/uploads/2020/03/PTJA09-brolucizumab-Core-Submission-Dossier-by-Novartis-v1.0.pdf.*
2. *Flaxel CJ, Adelman RA, Bailey ST, et al. Age-Related Macular Degeneration Preferred Practice Pattern®. Ophthalmology 2020;127:P1-P65.* Crossref
3. *Regeneron. Eylea ® prescribing information. Available from: https://www.regeneron.com/downloads/eylea_fpi.pdf.*
4. *Genentech. Lucentis ® prescribing information. Available from: https://www.gene.com/download/pdf/lucentis_prescribing.pdf.*
5. *Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. Ann Pharmacother 2007;41:614-25.* Crossref
6. *Kiss S, Liu Y, Brown J, et al. Clinical monitoring of patients with age-related macular degeneration treated with intravitreal bevacizumab or ranibizumab. Ophthalmic Surg Lasers Imaging Retina 2014;45:285-91.* Crossref
7. *Boulanger-Scemama E, Querques G, About F, et al. Ranibizumab for exudative age-related macular degeneration: a five year study of adherence to follow-up in a real-life setting. J Fr Ophtalmol 2015;38:620-7.* Crossref

8. *Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. Br J Ophthalmol 2015;99:220-6.* Crossref
9. *Kim LN, Mehta H, Barthelmes D, Nguyen V, Gillies MC. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. Retina 2016;36:1418-31.* Crossref
10. *Ehlken C, Helms M, Böhringer D, Agostini HT, Stahl A. Association of treatment adherence with real-life VA outcomes in AMD, DME, and BRVO patients. Clin Ophthalmol 2017;12:13-20.* Crossref
11. *MacCumber MW. Real-world injection intervals in wet AMD. Retina Today 2020:20-2.*
12. *Buckle M, Donachie PH, Johnston RL. Long-term outcomes of intravitreal ranibizumab for neovascular age-related macular degeneration in a well defined region of the UK. Br J Ophthalmol 2016;100:240-5.* Crossref
13. *Freund KB, Mrejen S, Gallego-Pinazo R. An update on the pharmacotherapy of neovascular age-related macular degeneration. Expert Opin Pharmacother 2013;14:1017-28.* Crossref
14. *Novartis. BEOVU ® prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf.*
15. *Nelson AL. Antibody fragments: hope and hype. MAbs 2010;2:77-83.* Crossref
16. *Tadayoni R, Sararols L, Weissgerber G, Verma R, Clemens A, Holz FG. Brolucizumab: a newly developed anti-VEGF molecule for the treatment of neovascular age-related macular degeneration. Ophthalmologica 2021;244:93-101.* Crossref
17. *Gaudreault J, Gunde T, Floyd HS, et al. Preclinical pharmacology and safety of ESBA1008, a single-chain antibody fragment, investigated as potential treatment for age related macular degeneration. Invest Ophthalmol Vis Sci 2012;53:3025.*
18. *Tietz J, Spohn G, Schmid G, et al. Affinity and potency of RTH258 (ESBA1008), a novel inhibitor of vascular endothelial growth factor A for the treatment of retinal disorders. Invest Ophthalmol Vis Sci 2015;56:1501.*
19. *Holz FG, Dugel PU, Weissgerber G, et al. Single-chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration: a randomized controlled study. Ophthalmology 2016;123:1080-9.* Crossref
20. *Szabó E, Phillips DJ, Droste M, et al. Antitumor activity of DLX1008, an anti-VEGFA antibody fragment with low picomolar affinity, in human glioma models. J Pharmacol Exp Ther 2018;365:422-9.* Crossref
21. *Nimz EL, Van't Land CW, Yáñez JA, Chastain JE. Intraocular and systemic pharmacokinetics of brolucizumab (RTH258) in nonhuman primates. Invest Ophthalmol Vis Sci 2016;57:4996.*
22. *Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2020;127:72-84.* Crossref
23. *Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2021;128:89-99.* Crossref
24. *Lally D. An assessment of BCVA and CST outcomes with brolucizumab and aflibercept in patients with early persistent retinal fluid: 96 week pooled data from HAWK and HARRIER. Presented at: European Society of Retina Specialists 2020 Congress. October 2020.*
25. *Sharma A, Kumar N, Parachuri N, et al. Brolucizumab—early real-world experience: BREW study. Eye (Lond) 2021;35:1045-7.* Crossref
26. *Bulirsch LM, Saßmannshausen M, Nadal J, Liegl R, Thiele S, Holz FG. Short-term real-world outcomes following intravitreal brolucizumab for neovascular AMD: SHIFT study. Br J Ophthalmol 2022;106:1288-94.* Crossref
27. *Chakraborty D, Maiti A, Sheth JU, et al. Brolucizumab in neovascular age-related macular degeneration: Indian real-world experience: the BRAILLE study. Clin Ophthalmol 2021;15:3787-95.* Crossref
28. *Panigrahi PK. A case of recalcitrant neovascular wet age-related macular degeneration treated with intravitreal brolucizumab. Photodiagnosis Photodyn Ther 2021;35:102450.* Crossref
29. *Bilgic A, Kodjikian L, March de Ribot F, et al. Real-world experience with brolucizumab in wet age-related macular degeneration: the REBA study. J Clin Med 2021;10:2758.* Crossref
30. *Avaylon J, Lee S, Gallemore RP. Case series on initial responses to intravitreal brolucizumab in patients with recalcitrant chronic wet age-related macular degeneration. Int Med Case Rep J 2020;13:145-52.* Crossref
31. *Member update: Novartis-appointed safety review committee reports initial brolucizumab findings. Available from: https://www.brolucizumab.info/sites/brolucizumab_info/files/2020-07/ASRS_SRC_report.pdf.*
32. *Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion-related events with brolucizumab: post hoc review of HAWK and HARRIER. Ophthalmology 2021;128:1050-9.* Crossref
33. *Baumal CR, Bodaghi B, Singer M, et al. Expert opinion on management of intraocular inflammation, retinal vasculitis, and vascular occlusion after brolucizumab treatment. Ophthalmol Retina 2021;5:519-27.* Crossref
34. *Sharma A, Kumar N, Parachuri N, et al. Brolucizumab—foreseeable workflow in the current scenario. Eye (Lond) 2021;35:1548-50.* Crossref
35. *Khoramnia R, Figueroa MS, Hattenbach LO, et al. Manifestations of intraocular inflammation over time in patients on brolucizumab for neovascular AMD. Graefes Arch Clin Exp Ophthalmol 2022;260:1843-56.* Crossref
36. *Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. Ophthalmology 2020;127:1345-59.* Crossref
37. *Haug SJ, Hien DL, Uludag G, et al. Retinal arterial occlusive vasculitis following intravitreal brolucizumab administration. Am J Ophthalmol Case Rep 2020;18:100680.* Crossref
38. *Khanani AM, Zarbin MA, Barakat MR, et al. Safety outcomes of brolucizumab in neovascular age-related macular degeneration: results from the IRIS Registry and Komodo Healthcare Map. JAMA Ophthalmol 2022;140:20-28.* Crossref
39. *Maruko I, Okada AA, Iida T, et al. Brolucizumab-related intraocular inflammation in Japanese patients with age-related macular degeneration: a short-term multicenter study. Graefes Arch Clin Exp Ophthalmol 2021;259:2857-9.* Crossref
40. *Ogura Y, Jaffe GJ, Cheung CMG, et al. Efficacy and safety of brolucizumab versus aflibercept in eyes with polypoidal choroidal vasculopathy in Japanese participants of HAWK. Br J Ophthalmol 2022;106:994-9.* Crossref

Three-dimensional digital heads-up microscope for ophthalmic microsurgery

Nicholas Fung[1], FHKAM, FCOphHK, MRCS, MBChB; Tiffany Chan[2]; Rachel Cheung[3], MBBS
[1]Department of Ophthalmology, Faculty of Clinical Medicine, The University of Hong Kong, Hong Kong SAR, China
[2]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
[3]Hong Kong West Cluster, Hospital Authority, Hong Kong SAR, China

Correspondence and reprint requests:
Dr Nicholas Fung, Department of Ophthalmology, The University of Hong Kong, Hong Kong SAR, China. Email: nfung@hku.hk

Abstract

The use of the three-dimensional (3D) digital heads-up microscope is increasingly popular in ophthalmology. Its advantages include improved depth of field, excellent visualization, lower illumination requirements, better ergonomics, and more effective teaching. A pilot study involving 18 ophthalmologists was conducted to compare the 3D microscope with the traditional optical microscope in performing microsurgical steps. Although the mean total operating time to complete five tasks was longer using the 3D microscope than the optical microscope (545 vs 410 seconds, p=0.0009), a downward trend was observed for the mean duration for each task using the 3D microscope. The rapid learning curve reflects the ease of learning and fast adaptation to the new instrument. Operating times may improve with more practice.

Key words: Imaging, Three-Dimensional; Microscopy; Microsurgery; Ophthalmologists

Background

Use of the three-dimensional (3D) digital heads-up microscope is increasingly popular in the field of ophthalmic microsurgery. It allows surgeons to view stereoscopic 3D images on a large high-definition monitor in a heads-up position rather than peering through the oculars of a microscope.[1]

3D display systems can be classified as active or passive systems.[2] An active system shows alternating consecutive images for the right and left eyes rapidly; special electronic glasses are required to actively suppress the image in the contralateral eye. It is mostly used for head-mounted systems. In a passive system, two images are mixed horizontally and then split and viewed by polarized glasses.[2] The passive system is used in commercially available display systems including the ZEISS ARTEVO 800 (Carl Zeiss Meditec, Jena, Germany) and the NGENUITY 3D Visualization System (Alcon, Fort Worth [TX], USA)

The use of 3D heads-up display systems in cataract surgery was first reported by Weinstock et al.[3] Other applications include Descemet's membrane endothelial keratoplasty,[4] strabismus surgery,[5] glaucoma surgery,[6] and vitrectomy.[1]

The ZEISS ARTEVO 800 microscope was introduced in 2019 and launched in North America, Germany, and the United Kingdom over the course of 2020. In March 2020, The University of Hong Kong was among the first places in Asia to use the microscope. Unlike the NGENUITY 3D Visualization System in which a video system is adapted to optical microscopes, the ZEISS ARTEVO 800 has a built-in digital and optical system. This enables a higher resolution sensor, integrated optical coherence tomography, simultaneous optical and digital viewing, and a much shorter lag time. Additionally, the absence of an external camera enables an unobstructed view of the screen.

With regard to optics, it offers a digital view that enables the full performance of cameras, enhanced depth perception, and higher resolution. It reduces the illumination level requirements and the associated risk of phototoxicity.[7] The

ZEISS ARTEVO 800 comes with two integrated three-chip 4K cameras and a 4K monitor. The 3D system can show multiple displays simultaneously such as real-time optical coherence tomography scans and the digital overlay of data, providing live feedback to aid intraoperative decision-making.[8] Moreover, the ZEISS ARTEVO 800 has an auto-adjust function and a contact-free fundus viewing system, which helps improve surgeons' workflow. It can switch to traditional optical viewing if the surgeon chooses, providing a simultaneous 3D heads-up perspective as well.

Heads-up surgery allows for greater freedom of posture and better ergonomics while manipulating surgical instruments, compared with traditional methods, as surgeons view the microscope's images on a panel display in a more natural stance (**Figure**).[9] It minimizes neck and lower-back fatigue and musculoskeletal injuries related to unnatural postures. For educational purposes, 3D animated ophthalmic surgery teaching effectively improved students' practical and theoretical understanding. Medical students and ophthalmologist trainees are more accepting of learning this way than via traditional surgical videos.[10]

Methods

A pilot study involving 18 ophthalmologists (ranging from second-year trainees to consultants) was conducted to compare the 3D digital heads-up microscope with the traditional optical microscope. Ophthalmologists with prior experience with 3D viewing systems were excluded. A standardized introductory course on video-assisted 3D technology was given. A maximum of five doctors were tested in each session to maximize exposure and minimize variations. Pedal use, 3D set-up, and microscope functions were also taught.

Figure. Surgeons viewing the microscope images on a panel display in a more natural stance.

Participants were asked to suture and tie knots with 10-0 nylon and graft with 7-0 Vicryl five times using either the 3D microscope or the optical microscope. They then performed the same tasks another five times using the alternate microscope. All attempts were timed and recorded. Their performances were independently assessed by two blinded consultant surgeons via recorded videos using the Objective Structured Assessment of Technical Skills rating scale. Parameters assessed included respect for tissue, time and motion, instrument handling, flow of operation, knot quality, suture placement, and comfort rating of the surgeon.

Participants were asked to rate their satisfaction of the illumination, size of the television screen, and screen distance. They were also asked to compare viewing, ergonomics, ease of task, and ease of microscope operation for the two systems. The learning curve of the 3D microscope and the performance of the microsurgical task were assessed. Student's *t* test was used to compare the participants' ratings of the two systems.

Results

The mean total operating time to complete five tasks was longer using the 3D microscope than the optical microscope (545 vs 410 seconds, p=0.0009), regardless of which microscope was used first. This is because doctors are trained and have more experience using the optical microscope. Nonetheless, a downward trend was observed for the mean duration for each task using the 3D microscope. The first task took 117 seconds on average; the time decreased to 95 seconds for the fifth task. Tasks were performed consecutively; the rapid learning curve reflects the ease of learning and fast adaptation to the new instrument. Operating times may improve with more practice.

The overall Objective Structured Assessment of Technical Skills scores for the 3D microscope and the optical microscope were comparable in all aspects. Surgeons with >10 years post-fellow experience displayed better surgical performance when using the 3D microscope in terms of knot quality, suture placement, and comfort rating. Similarly, surgeons with 2 to 10 years post-fellow experience displayed better surgical performance when using the 3D microscope in terms of respect for tissue, instrument handling, and comfort rating. However, surgeons with <2 years post-fellow experience received lower performance scores in all categories when using the 3D microscope. More training should be provided to younger surgeons to facilitate their transition from the optical microscope to the 3D microscope.

Participants were satisfied with the television screen size and screen distance, with a mean score of 4.50 and 4.39 out of 5, respectively. Surgeons with >10 years post-fellow experience reported better ergonomics when using the 3D microscope (p=0.025). Most participants reported the 3D microscope to be equivalent or superior to the optical microscope in terms of viewing (61%) and ease of microscope operation (78%). Yet, more than half of participants gave the optical microscope a higher rating in ease of task. This could be biased by their previous training and surgical experiences with optical microscopes.

Conclusion

The 3D heads-up microscope has improved depth of field, excellent visualization, lower illumination requirements, and ergonomic advantages. Although there is an initial learning curve, the ease of manipulation and the speed with which people adapt to the new instrument suggest that ophthalmologists can be accustomed to using the 3D microscope quickly even when they were first trained on an optical microscope.

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

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The ZEISS ARTEVO 800 microscope was purchased by grants of NF and donation to The University of Hong Kong.

Data availability

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

Acknowledgements

The authors thank Lam Wai Ching and Jonathan Chan for their assistance in reviewing the surgical videos.

References

1. *Eckardt C, Paulo EB. Heads-up surgery for vitreoretinal procedures: an experimental and clinical study. Retina 2016;36:137-47.* Crossref
2. *Martínez-Toldos JJ, Fernández-Martínez C, Navarro-Navarro A. Experience using a 3D head-mounted display system in ophthalmic surgery. Retina 2017;37:1419-21.* Crossref
3. *Weinstock RJ. Operate with your head up. Cataract Refract Surg Today 2011;66:8.*
4. *Galvis V, Berrospi RD, Arias JD, Tello A, Bernal JC. Heads up Descemet membrane endothelial keratoplasty performed using a 3D visualization system. J Surg Case Rep 2017;2017:rjx231.* Crossref
5. *Hamasaki I, Shibata K, Shimizu T, Kono R, Morizane Y, Shiraga F. Lights-out surgery for strabismus using a heads-up 3D vision system. Acta Med Okayama 2019;73:229-33.*
6. *Palácios RM, de Carvalho ACM, Maia M, Caiado RR, Camilo DAG, Farah ME. An experimental and clinical study on the initial experiences of Brazilian vitreoretinal surgeons with heads-up surgery. Graefes Arch Clin Exp Ophthalmol 2019;257:473-83.* Crossref
7. *Adam MK, Thornton S, Regillo CD, Park C, Ho AC, Hsu J. Minimal endoillumination levels and display luminous emittance during three-dimensional heads-up vitreoretinal surgery. Retina 2017;37:1746-9.* Crossref
8. *Ehlers JP, Modi YS, Pecen PE, et al. The DISCOVER study 3-year results: feasibility and usefulness of microscope-integrated intraoperative OCT during ophthalmic surgery. Ophthalmology 2018;125:1014-27.* Crossref
9. *Moura-Coelho N, Henriques J, Nascimento J, Medeiros MD. Three-dimensional display systems in ophthalmic surgery: a review. Eur Ophthalmic Rev 2019;13:31-6.* Crossref
10. *Prinz A, Bolz M, Findl O. Advantage of three dimensional animated teaching over traditional surgical videos for teaching ophthalmic surgery: a randomised study. Br J Ophthalmol 2005;89:1495-9.* Crossref

PHOTO ESSAY

Guided tour to the hyperbaric oxygen therapy center in Hong Kong

Sunny Chi Lik Au[1,2], *MB ChB, MRCSEd(Ophth), AFCOphthHK*
[1]*Department of Ophthalmology, Tung Wah Eastern Hospital, Hong Kong SAR, China*
[2]*Department of Ophthalmology, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China*

Key words: *Hyperbaric oxygenation; Retinal artery occlusion*

On 29 September 2022, a guided tour to the hyperbaric oxygen therapy (HBOT) center at the Pamela Youde Nethersole Eastern Hospital was held. Central retinal artery occlusion (CRAO), also known as ocular stroke, is an ophthalmic emergency that may result in blindness.[1,2] Its treatments include breathing into a paper bag, carbogen inhalation,[3] intraocular pressure lowering medications, ocular massage, anterior chamber paracentesis,[4] thrombolysis,[5] and HBOT.[6] In 2018, the HBOT center was set up for treatment of CRAO.[6,7]

The HBOT center is equipped with multiple chambers (Haux-Starmed-Quadro 3300-2300) with three locks: main lock, emergency lock, and intensive care unit lock (**Figure 1**). The entire chamber is measured 13 m (length) × 3.8 m (width) × 2.8 m (height) and weighed about 100 tonnes; it has a maximum capacity of 16 patients. Most patients with CRAO are ambulatory with no ventilation problems and are treated in a chamber where patients sit on the sofa and wear a transparent hood that delivers 100% oxygen for breathing, while the chamber is pressurized

Figure 1. (a) An overview of the three locks of the hyperbaric oxygen chamber. (b) The chamber for ambulatory patients with central retinal artery occlusion who sit on the sofa and wear a transparent hood that delivers oxygen during treatment. (c) A stretcher is placed in the intensive care unit lock. Balloons are used to demonstrate pressurization and depressurization. (d) A toilet is located behind the orange curtain. Patients are kept under pressurization while going to toilet.

Figure 2. An enabling lock in the hyperbaric oxygen chamber.

Figure 3. Control station with control panels for opening/closing of doors, working pressures of the chamber, breathing gas (air/oxygen), humidity, temperature, cooling/heating, and fire extinguishing system. Live videos inside the chamber are also displayed.

Figure 4. The manual control panel is used in case the computer control system breaks down.

Figure 5. Monitor display of parameters of desired and actual pressure, gradient, oxygen concentration, and temperature.

according to protocols. Patients can watch television through the transparent hood. Patients can go to the adjacent equally pressurized chamber for toilet needs. There is an enabling lock for transporting medications, intravenous fluid, glucose monitor device, and dressing materials into and out of the chamber without pressure break. It is a small chamber where pressure inside is adjusted according to the side it is opened (**Figure 2**).

There are several important parameters for operating the HBOT chamber: desired and actual pressure in kPa, gradient in kPa/min, and oxygen concentration in %. Temperature is less important; it changes with pressure. These parameters are monitored and recorded by computers at the control station (**Figure 3**). Contingency manual control is feasible in case of machine failure (**Figure 4**), but smooth transition of parameters by hands is difficult. There is a control panel to display opening/closing of doors, working pressures of the chamber, breathing gas (air/oxygen), humidity, temperature, cooling/heating, and fire extinguishing system. Display of these parameters can be projected to the hall display (**Figure 5**). Live videos inside the chamber are also displayed. During the guided tour, balloons were used to

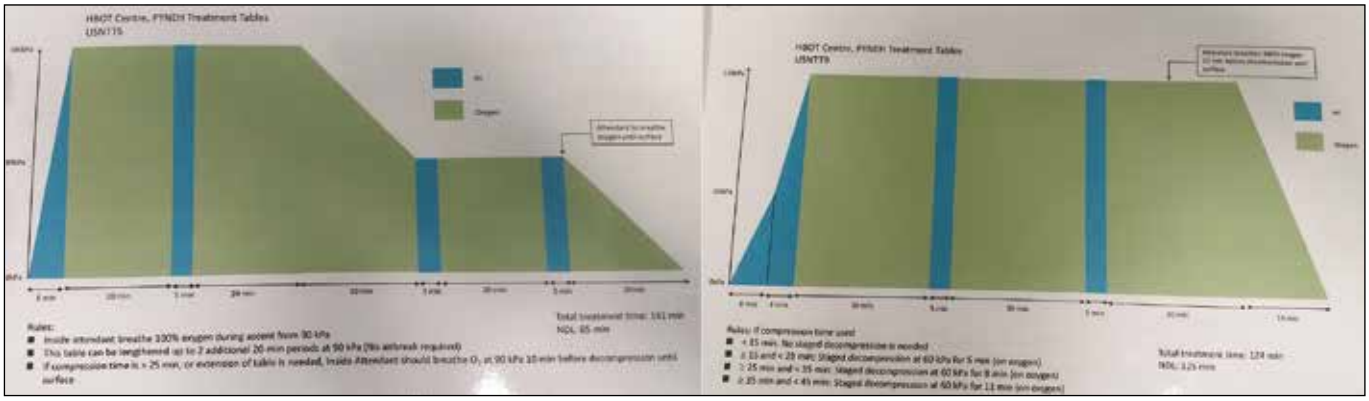


Figure 6. The United States Navy Treatment Tables 5 and 9.

demonstrate chamber pressurization; balloons shrank upon pressurization and expand upon decompression.

The 5-day HBOT for CRAO is based on the guidelines of the Undersea and Hyperbaric Medical Society[8] and the United States Navy Treatment Tables (**Figure 6**). For patients undergoing the first HBOT, Treatment Table 5 algorithm is used. Pressure is increased to 180 kPa, with three air-breaks in-between. The treatment session takes 141 minutes. For subsequent twice-daily treatment, Treatment Table 9 algorithm is used. Pressure is increased to 136 kPa, with two air-breaks. The treatment session takes 124 minutes. The entire treatment requires 10 sessions of HBOT.

Vitals are measured before and after HBOT. During pressurization, patients may feel discomfort in ears when ear pressure increases. Maneuvers to equalize pressure such as mouth opening and saliva swallowing are taught by nurses. If these maneuvers fail, an Otovent is used, which is a balloon attached to the nose. Patients are instructed to blow up the Otovent through a nostril while pressing the other nostril closed with a finger. If difficulties persist or signs of barotrauma appear, HBOT is ceased for myringotomy. During HBOT, when pressure plateau is reached, patients usually do not feel anything special. Frequency of monitoring depends on premorbidity and conditions of patients on site. Blood glucose level is usually monitored, as hypoglycemia can occur during HBOT. Vitals are checked again before discharge.

Basic physics on hyperbaric medicine were introduced to visitors. The Henry's law states that the amount of gas that dissolves in a liquid is directly proportional to the partial pressure of that gas above the liquid. The Dalton's law states that the total pressure exerted by a mixture of gases is equal to the sum of the pressures exerted by each gas if it alone occupies the total volume. For example, if a patient is breathing a mixture of 40% oxygen at 180 kPa, the partial pressure of oxygen is 72 kPa.

Contributor

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

As an editor of the journal, SCLA was not involved in the peer review process and has disclosed no other conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

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

References

1. *Flaxel CJ, Adelman RA, Bailey ST, et al. Retinal and Ophthalmic Artery Occlusions Preferred Practice Pattern. Ophthalmology 2020;127:P259-P287.* Crossref
2. *Au SCL, Ko CKL. Ocular stroke and COVID-19. Hong Kong Med J 2021;27:231.* Crossref
3. *Varma DD, Cugati S, Lee AW, et al. A review of central retinal artery occlusion: clinical presentation and management. Eye (Lond) 2013;27:688-97.* Crossref

4. *Cugati S, Varma DD, Chen CS, et al. Treatment options for central retinal artery occlusion. Curr Treat Options Neurol 2013;15:63-77.* Crossref
5. *Dumitrascu OM, Newman NJ, Biousse V. Thrombolysis for central retinal artery occlusion in 2020: time is vision! J Neuroophthalmol 2020;40:333-45.* Crossref
6. *Au SCL, Chong SSY, Leow PL, et al. Efficacy and safety of hyperbaric oxygen therapy for acute central retinal artery occlusion in Hong Kong: results of the first 3 years. Hong Kong J Ophthalmol 2020;26:6-9.* Crossref
7. *Leung JK, Lam RP. Hyperbaric oxygen therapy: its use in medical emergencies and its development in Hong Kong. Hong Kong Med J 2018;24:191-9.* Crossref
8. *Murphy-Lavoie H, Butler F, Hagan C. Central retinal artery occlusion treated with oxygen: a literature review and treatment algorithm. Undersea Hyperb Med 2012;39:943-53.*

ONE POWERFUL DROP TODAY[1-4]

could create a life full of possibilities tomorrow.[5–10]

Treat with power.[1–4] Treat with confidence.[11]

Step-up to GANFORT®

(bimatoprost/timolol ophthalmic solution) 0.03%/ 0.5%

GANFORT™ GANfort® Pf

Available in bottles and **preservative-free** unit doses.[1]

Ganfort®/ Ganfort® Pf Abbreviated Product Information
Active Ingredient & Strength: GANFORT® bimatoprost 0.3 mg/mL + timolol 5 mg/mL eye drops, solution. GANFORT® PF bimatoprost 0.3 mg/mL + timolol 5 mg/mL eye drops, solution, without preservative. **Indication:** Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues. **Dosage and method of use:** The recommended dose for adult is one drop of GANFORT® in the affected eye(s) once daily, administered either in the morning or in the evening. It should be administered at the same time each day. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, not controlled with pace-maker. Overt cardiac failure, cardiogenic shock. **Warning and Precautions:** Like other topically applied ophthalmic medicinal products, the active substances (timolol/ bimatoprost) in GANFORT® may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed with GANFORT®. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions (ADRs) as seen with systemic beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. **Adverse Events:** Very Common: conjunctival hyperaemia. Common: headache, dizziness, punctuate keratitis, corneal erosion, burning sensation, conjunctival irritation, eye pruritus, stinging sensation in the eye, foreign body sensation, dry eye, erythema of eyelid, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, visual acuity worsened, blepharitis, eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes. Rhinitis, blepharal pigmentation, hirsutism, skin hyperpigmentation (periocular). Uncommon: Iritis, conjunctival oedema, eyelid pain, abnormal sensation in the eye, asthenopia, trichiasis, iris hyperpigmentation, deepening of eyelid sulcus, eyelid retraction, eyelash discolouration (darkening), dyspnoea. Not Known: hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy, Insomnia, nightmare, Dysgeusia, cystoid macular oedema, eye swelling, vision blurred, bradycardia, bronchospasm (predominantly in patients with pre-existing bronchospastic disease), asthma, Alopecia, fatigue. **Please read the full prescribing information before prescribing. Full prescribing information is available upon request.**

HK_API GANFORT/ GANFORT PF (May 2019)
For healthcare professionals only.
Adverse event should be reported to AbbVie pharmacovigilance team at drugsafety.pv@abbvie.co

References:
1. GANFORT®. Hong Kong Prescribing Information, MAY 2019. 2. Pfennigsdorf S et al. Clin Ophthalmol 2013; 7: 1219–1225. 3. Pfennigsdorf S et al. Clin Ophthalmol 2016; 10: 1837–1846. 4. Yilmaz SG et al. Int Ophthalmol 2018; 38(4): 1425–1431. 5. Lichter PR et al. Ophthalmology 2001; 108(11): 1943–1953. 6. Leske MC et al. Ophthalmology 2007; 114(11): 1965–1972. 7. CNTGS. Am J Ophthalmol 1998; 126(4): 487–497. 8. Yue Wang MD et al. Medicine 2017; 96(48): e8019. 9. Peters D et al. Acta Ophthalmologica 2015; 93: 745-752. 10. Sun X et al. Patient Prefer Adherence 2017; 11: 845–852. 11. Allergan. Unpublished Data. [DOF1 – INT-NON-2051227] 2020.

Allergan an AbbVie company

Address: Suite 2404, 24/F, AIA Tower,
183 Electric Road, North Point, Hong Kong
Phone: (852) 2610 2525
Fax: (852) 2219 7397

Produced by Allergan, an AbbVie company.
HK-GAN-230002 07/ Feb/ 2023

enVista®

one-piece hydrophobic acrylic intraocular lens

enVista® toric

One-piece Hydrophobic Acrylic Toric Intraocular Lens

The Design is Distinctive.

The Outcomes Are Clear.

More than 3 million eyes already enjoying the enVista® experience worldwide[1]

1. Data on file, Bausch & Lomb. enVista® and Enhanced enVista® data in 2013 - Q1 2020

HK-SU-2022-12-011

Bausch & Lomb (HK) Ltd.
Suites 3901 & 3912-14, 39/F, Tower 6, The Gateway, 9 Canton Road, Tsim Sha Tsui, Kowloon, Hong Kong. Tel: +852 2213 3333

CATARACT LASER RETINA

BAUSCH + LOMB
See better. Live better.

LUXSMART™

PRELOADED

PURE

Refractive Optics

HYDROPHOBIC IOL

The extended depth of focus intraocular lens for your daily range of vision

HYDROPHOBIC PRO TECHNOLOGY* PRELOADED EDOF

Scan this QR code to have additional information about LuxSmart™

* PRO TECHNOLOGY: Pure refractive Optics Technology

HK-SU-2022-10-004

Bausch & Lomb (HK) Ltd.
Suites 3901 & 3912-14, 39/F, Tower 6, The Gateway, 9 Canton Road, Tsim Sha Tsui, Kowloon, Hong Kong Tel: +852 2213 3333

CATARACT LASER RETINA

BAUSCH+LOMB
See better. Live better.

VYZULTA™
(latanoprostene bunod ophthalmic solution),0.024%

20 YEARS
OF BREAKTHROUGH IN GLAUCOMA TREATMENT

Indication

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1]

One molecule, two pathways

Lowers IOP by increasing outflow through both the trabecular meshwork and uveoscleral pathway[1]

Remarkable efficacy

Reduced the mean IOP up to 9.0 mmHg from baseline[2*]

Demonstrated safety

<1% discontinuation rate due to ocular adverse effects[1]

***VOYAGER study design:** a randomized, parallel-group, phase 2 study, which compared the efficacy and safety of 4 doses of VYZULTA™ and latanoprost 0.005% in 413 patients with open-angle glaucoma or ocular hypertension. Primary endpoint was the change of mean diurnal IOP at day 28 from baseline. The mean IOP at baseline was 26.0 mmHg in the VYZULTA™ 0.024% group and 26.2 mmHg in the latanoprost 0.005% group.[2]

IOP=intraocular pressure.

References: 1. VYZULTA Hong Kong prescribing information. **2.** Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. Br J Ophthalmol 2015; 99(6): 738-45.

INDICATION VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. **DOSAGE AND AMINISTRATION** The recommended dosage is one drop in the conjunctival sac of the affected eye(s) once daily in the evening. Do not administer VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% more than once daily since it has been shown that more frequent administration of prostaglandin analogs may lessen the intraocular pressure lowering effect. If VYZULTA™ is to be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure, administer each drug product at least five (5) minutes apart. **IMPORTANT SAFETY INFORMATION** • Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent. • Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation. • Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA™ should generally not be used in patients with active intraocular inflammation. • Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. • There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients. • Contact lenses should be removed prior to the administration of VYZULTA™ and may be reinserted 15 minutes after administration. • The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation. Please refer to full package insert for the detail.

For healthcare professional only.
Please refer to full Prescribing Information and additional Important Safety Information for VYZULTA™.

BAUSCH + LOMB
See better. Live better.

Bausch & Lomb (H.K.) Ltd.
Suites 3901 & 3912-14, 39/F
Tower 6, The Gateway, 9 Canton Road
Tsim Sha Tsui, Kowloon, Hong Kong
Tel: (+852) 2213 3333

REDUCTION OF ELEVATED INTRAOCULAR PRESSURE
IN PATIENTS WITH OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION

Monopost®

Eye drops solution in single dose container

Latanoprost 0.005%

The first preservative-free latanoprost formulation[1]

with PROVEN[2] EFFICACY

U.S. FDA APPROVED

- **N°1** Prostaglandin in Europe[1]
- Supported by **22 publications**[3]
- More than **1 million patients** treated with Monopost® every month in more than **40 countries**[4]
- Good tolerability profile
- Innovative & preservative-free formulation
- Stored at room temperature

HMS-MNPTHEA-AD/202304

HMS WORLD'S LOCAL PARTNER

For further information:
Hongkong Medical Supplies Ltd.
Tel: 2806 3112 Fax: 2887 3425
E-mail: sales@hkmedsup.com.hk
Website: www.hongkongmedical.com.hk

REFERENCES

1. Market Data August 2022 (SU and Values). 2. Rouland JF. et al. Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. Br J Ophtalmol 2013;97(2):196-200.5. DOI: 10.1136/bjophthalmol-2012-302121. 3. Data available upon request. 4. Laboratoires Théa, internal data, August 2022.

Théa let's open our eyes

FOR PATIENTS WITH DRY EYES

THEALOZ® DUO

TREHALOSE 3% | HYALURONIC ACID 0.15%

MEDICAL DEVICE IIb

TREHALOSE 3%

HYALURONIC ACID 0.15%

PROTECTION, HYDRATION AND LUBRICATION OF THE EYE, FOR TREATMENT OF MODERATE TO SEVERE DRY EYE SYNDROME

- **Increases tear film thickness and tear break-up time[1,2]**
- **Provides greater improvements in dry eye symptoms[3]**
- **Reduces tear film inflammatory biomarkers[4]**
- **Allows a better recovery after cataract surgery[5]**

Properties:

AS FEATURED IN tfos DEWS II

- **Preservative-free**

  Highly Recommended in TFOS DEWS II Report:

  Preservative-free preparations are preferred when patients need frequent instillation of eye drops[6]
- **Hypotonic formulation**
- **Phosphate-free**
- **Multidose ABAK® bottle**

  Up to 3 months of use after opening

Suitable for:

- Adults
- Children
- Pregnant or breastfeeding women
- Contact lens wearers

HMS WORLD'S LOCAL PARTNER

For further information:
Hongkong Medical Supplies Ltd.
Tel: 2806 3112 Fax: 2887 3425
E-mail: sales@hkmedsup.com.hk
Website: www.hongkongmedical.com.hk

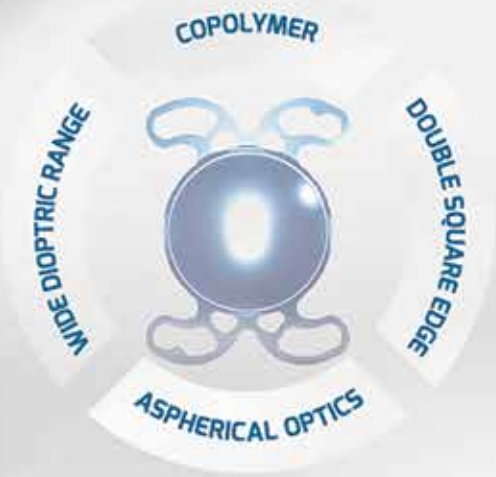
Théa let's open our eyes

References:
1. Thealoz® Duo clinical study for CE mark file 2012. 2. Schmidl D., Schmetterer L., Witkowska KJ. et al. Tear film thickness after treatment with artificial tears in patients with moderate dry eye disease. Cornea 2015;34(4):421-6. 3. Pinto-Bonilla JC et al. A Randomised Cross Over Comparison of Trehalose/Hyaluronate Eye Drops and Standard Treatment: Patient Satisfaction in the Treatment of Dry Eye Syndrome. Ther Clin Risk Manag 2015;11:595-603. 4. Fariselli C. et al. Trehalose/hyaluronate eyedrop effects on ocular surface inflammatory markers and mucin expression in dry eye patients. Clinical Ophthalmology 2018:12 1293–1300. 5. Balta, Ö. & Telek, H. H. Effect of a Hyaluronate–Trehalose Solution on Ocular Comfort and Tear-Film Instability After Cataract Surgery. Izlek Akademik Dergi 2020;3(1):34-43. 6. Baudouin C et al. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010 Jul;29(4):312-34.

HMS-THEATD-AD/202304

mini READY 4
INTRAOCULAR LENS

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

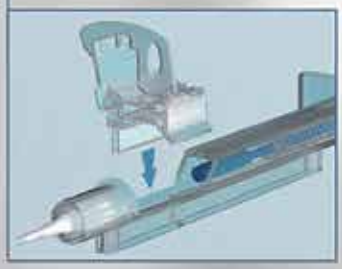


TECHNICAL SPECIFICATIONS

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 (0D to +40D) 119.9 (-3D to -1D)
Estimated A.C.D.	5.32 mm (0D 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

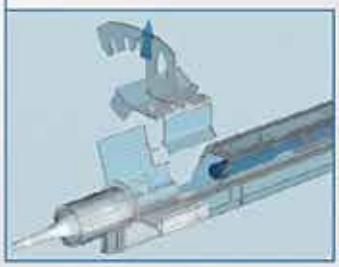
INSTRUCTION FOR USE OF THE PRELOADED VERSION

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.

CE 0123

www.affamed.com

AffaMed Technologies is the joint venture established between AffaMed and SIFI, to develop, manufacture and commercialize premium intraocular lenses (IOLs) in the Greater China market.

AffaMed Technologies

Primal Chemical Co., Ltd.
Tel: (852) 2343 3212
Fax: (852) 2797 8596
Email: info@primal.com.hk

EXTENDING THEIR HORIZONS

GIVE YOUR PATIENTS UNINTERRUPTED HIGH-QUALITY VISION

TRUE EXTENDED DEPTH OF FOCUS* FOR HIGH-QUALITY VISION[1,2]

- A unique, patented refractive lens design for sharp vision from far to near, including excellent intermediate distance vision[1,2]
- Consistent, uninterrupted performance in different lighting conditions over the full 24-hour day with negligible halos and glare[2-4]
- Excellent contrast sensitivity, even under mixed lighting conditions[1,3]

IN YOUR APPROPRIATELY SELECTED PATIENTS, YOU CAN NOW HAVE CONFIDENCE IN OFFERING UNINTERRUPTED, HIGH-QUALITY VISION AT ALL DISTANCES AND AT ALL TIMES

- EXCELLENT INTERMEDIATE AND FAR VISION, WITH GOOD NEAR VISUAL ACUITY
- NEGLIGIBLE HALOS AND GLARE
- CLOSELY MATCHES THE VISUAL RESULTS OF THE HUMAN EYE
- EXCELLENT CONTRAST SENSITIVITY, EVEN UNDER MIXED LIGHTING CONDITIONS

*EDOF

1. Savini G, et al. Visual performance of a new extended depth-of-focus intraocular lens compared to a distance-dominant diffractive multifocal intraocular lens. J Cataract Refract Surg. 2018;34(4):228-235.
2. Savini G, et al. Functional assessment of a new extended depth-of-focus intraocular lens. Eye (Lond). 2019;33(3):404-410.
3. Bellucci R, et al. Clinical and aberrometric evaluation of a new extended depth-of-focus intraocular lens based on spherical aberration. J Cataract Refract Surg. 2019;45(7):919-926.
4. Focus Study, Study code PSM15, data on file. SIFI.

CE 0123

www.affamed.com

AffaMed Technologies is the joint venture established between AffaMed and SIFI, to develop, manufacture and commercialize premium intraocular lenses (IOLs) in the Greater China market.

AffaMed Technologies

Primal Chemical Co., Ltd.
Tel: (852) 2343 3212
Fax: (852) 2797 8595
Email: info@primal.com.hk

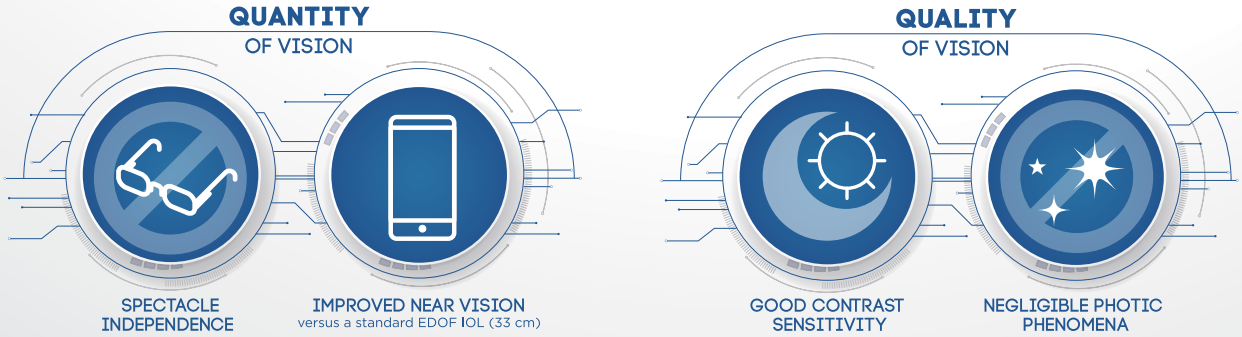
THE UNIQUE **WELL FUSION®** OPTICAL SYSTEM, WHICH COMBINES **MINI WELL®** AND **MINI WELL PROXA®**, OFFERS UNINTERRUPTED HIGH-QUALITY VISION, WITHOUT GLASSES.

well FUSION VISION UNINTERRUPTED

A UNIQUE OPTICAL SYSTEM BASED ON A COMPLEMENTARY OPTICS DESIGN USING THE SAME WAVEFRONT ENGINEERING TECHNOLOGY.[1,2]

WELL FUSION®

HAS BEEN DESIGNED TO PROVIDE PATIENTS WITH:



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.

CE 0123

www.affamed.com

AffaMed Technologies is the joint venture established between AffaMed and SIFI, to develop, manufacture and commercialize premium intraocular lenses (IOLs) in the Greater China market.

AffaMed Technologies

Primal Chemical Co., Ltd.
Tel: (852) 2343 3212
Fax: (852) 2797 8595
Email: info@primal.com.hk

VABYSMO® (Faricimab) 120mg/ml to 6mg/0.05ml solution for injection
Date of Preparation: June 2023
ABBREVIATED PRESCRIBING INFORMATION
Important note: Before prescribing, consult full prescribing information.

Abbreviated Product Information: Vabysmo Solution for Intravitreal Injection 6mg/0.05ml **Indications:** Vabysmo is indicated for the treatment of adult patients with neovascular (wet) age-related macular degeneration (nAMD) or visual impairment due to diabetic macular oedema (DMO). **Dosage and Administration:** *nAMD:* Recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks for the first 4 doses. Thereafter, an assessment of disease activity based on anatomic and/or visual outcomes is recommended 20 and/or 24 weeks after treatment initiation so treatment can be individualised. In patients without disease activity, administration of Vabysmo every 16 weeks should be considered. In patients with disease activity, treatment every 8 weeks or 12 weeks should be considered. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections. DMO: Recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks for the first 4 doses. Thereafter, treatment may be individualised using a treat-and-extend approach following an assessment of the individual patient's anatomic and visual outcomes. The dosing interval may be extended from every 4 to every 16 weeks, with extensions in increments of up to 4 weeks, based on the physician's judgement of the individual patient's anatomic and/or visual outcomes. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reductions of up to 8 weeks may be implemented if deemed necessary. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections. Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. Sterile equipment should be available in case paracentesis is required. Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. vision loss, eye pain, redness of the eye, photophobia, blurring of vision) without delay. For further information on dosage and administration, please refer to the local prescribing information. **Contraindications:** Patients with ocular or periocular infections, active intraocular inflammation, and with hypersensitivity to faricimab or to any of the excipients in Vabysmo. **Warnings and Precautions:** *Intravitreal injection-related reactions:* Intravitreal injections, including those with Vabysmo have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment and retinal tear. Proper aseptic injection techniques must always be used when administering Vabysmo. Patients should be instructed to report any symptoms, such as pain, loss of vision, photophobia, blurred vision, floaters, or redness, suggestive of endophthalmitis or any of the above-mentioned events without delay, to permit prompt and appropriate management. *Intraocular pressure increases:* Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including those with Vabysmo. Sustained (present at 2 or more consecutive visits) IOP increases > 21mm Hg have also been reported. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Vabysmo while the IOP is ≥ 30mm Hg). In all cases, both the IOP and perfusion of the optic nerve head must be monitored and managed appropriately. Special precaution is needed in patients with poorly controlled glaucoma. *Systemic effects:* Systemic adverse events including arterial thromboembolic events have been reported following intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors, including Vabysmo, and there is a theoretical risk that these may be related to VEGF inhibition. *Immunogenicity:* Patients should be instructed to inform their physician of any signs or symptoms or intraocular inflammation such as vision loss, eye pain, increased sensitivity to light, floaters or worsening eye redness, which might be a clinical sign attributable to hypersensitivity. *Bilateral treatment:* The safety and efficacy of Vabysmo administered in both eyes concurrently have not been studied. *Concomitant use of other anti-VEGF:* No data available on the concomitant use of Vabysmo with anti-VEGF medicinal products or other therapies (e.g., photodynamic therapy) for the treatment of nAMD or DMO in the same eye. Vabysmo should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular). *Retinal pigment epithelial tear:* Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for nAMD, include a large and/or high pigment epithelial detachment. Caution should be used in patients with risk factors for retinal pigment epithelial tears. Please refer to local prescribing information for the full information of warning and precautions. **Interactions:** No studies evaluating the drug interaction potential of Vabysmo have been performed. **Fertility, Pregnancy and Lactation:** Female patients of childbearing potential should use effective contraception during treatment with Vabysmo and for at least 3 months following the last intravitreal injection of Vabysmo. As a precautionary measure it is preferable to avoid the use of Vabysmo during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Vabysmo is not recommended during breast-feeding. **Undesirable Effects:** *Very common:* cataract; Common: conjunctival haemorrhage, intraocular pressure increased, vitreous floaters, retinal pigment epithelial tear (nAMD only), eye pain, lacrimation increased.Please refer to local prescribing for full list of undesirable effects.

Call for Reporting: If you have a suspected side effect or problem to report regarding one of our products, please contact or send the information to the Roche Patient Safety team via: (a) Email: hong_kong.drug_safety@roche.com, or (b) Phone: +852 2733 4711.

Please refer to VABYSMO PI for more details.

Roche Hong Kong Limited 22/F, FTLife Tower, 18 Sheung Yuet Road, Kowloon Bay Tel: +852 2723 2832
M-HK-00001282 valid until 7 June 2025 or until change is required in accordance with the regulatory requirements, whichever comes first.

*For VABYSMO abbreviated product information, please scan the QR code. Full product information will be provided upon request.

VABYSMO®
faricimab injection 6 mg

Alcon
Vision Suite

LuxOR Revalia™
OPHTHALMIC MICROSCOPE

Reveal the unexpected

Discover LuxOR® REVALIA™

Alcon's microscope for anterior and posterior procedures, delivering excellent visualization through proprietary ILLUMIN-i technology[1-4]:

33% Greater Depth of Field*[4]

6x larger, more stable, red reflex[2,4,5†]

Alcon Diagnostics & Phaco Integration[1,6,7]

* Compared to conventional focused illumination microscopes. Assuming 200 mm working distance, LuxOR Revalia adds 65 mm to the focal length, resulting in 33% increase vs a conventional 200mm microscope
† Compared to Z. Lumexx T, Lumexx 700, and Leixx M-820 microscopes

References
1. LuxOR Revalia User Manual 2. Cionni RJ, Pei R, Dimalanta R, et al. Evaluating red reflex and surgeon preference between nearly-collimated and focused beam microscope illumination systems. Transl Vis Sci Technol. 2015;4(4):7. 3. Alcon data on file, 2014. 4. Schwiegerling J & Dimalanta R. Depht of focus measurements of ophthalmic surgical microscopes. Poster presented at: The Association for Research in Vision and Ophthalmology; May 1-5, 2016; Seattle, WA. 5. Alcon drawing number 955-7210-004, 2014, Scientific Support Document, Communication for Alcon LuxOR Red Reflex and Depth of Focus Calculations. 6. Centurion Vision system User Manual. 7. Verion Digital Marker M User Manual

#1

AcrySof® IQ

PanOptix®

Presbyopia - Correcting IOL

Most-implanted Trifocal IOL Worldwide[1-5]

Over 2.2 million implants worldwide[1-5]

Excellent high-quality visual experience from far to near, with 99% patient satisfaction.[1]

References: 1. Modi S, et al. Visual and patient reported outcomes of a diffractive trifocal intraocular lens compared with those of a monofocal intraocular lens. Ophthalmology. 2021;128(2):197 207. **2.** ZHU et.al. Rate of Complete Spectacle Independence with a Trifocal IOL (PanOptix): A Systematic Literature Review and Meta Analysis. Presentation at 2022 ASCRS; April 2022; Washington, D.C. **3.** Market Scope 2022 IOL Market Report. **4.** Alcon Data on File, 2022. [REF 18881] 5) Clareon® PanOptix® Trifocal IOL Directions for Use.

AcrySof® IQ Vivity™
EXTENDED VISION IOL

Alcon
SEE BRILLIANTLY

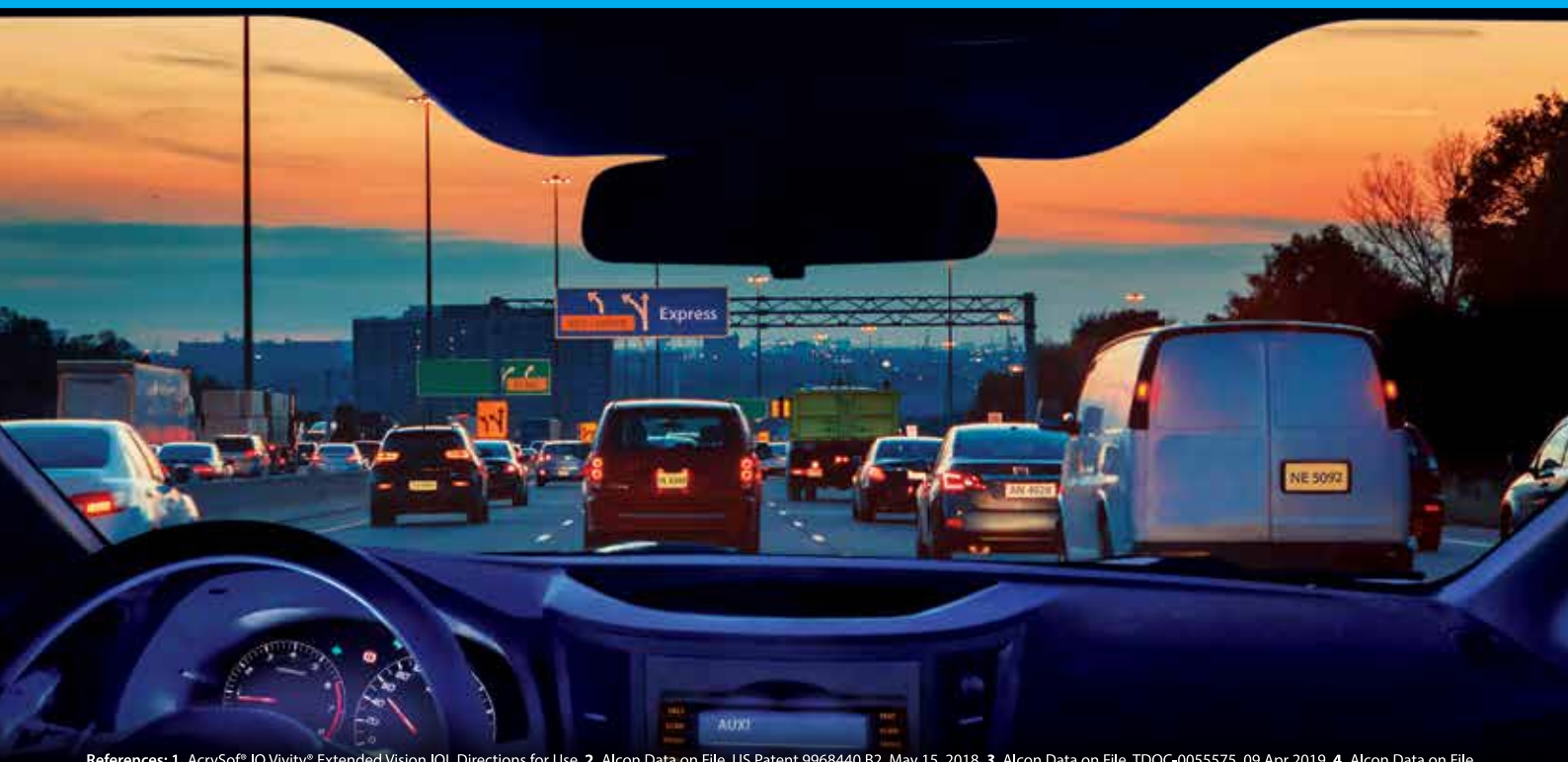
HK-ACP-2300008 App.202305 4iC_2822A

AcrySof® IQ Vivity™

First-of-Its-Kind Extended Vision IOL[1-4]

- **Monofocal-like visual disturbance profile**
- **Simplify the presbyopia-correcting experience for surgeons and patients[1-9]**

Patient-reported visual disturbances with AcrySof IQ Vivity were comparable to the AcrySof IQ IOL



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®, Symfony*, 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-surgery[1]paradigm/". Accessed Date 17.07.202

AcrySof® IQ Vivity™
EXTENDED VISION IOL

Alcon
SEE BRILLIANTLY

HK-ACP-2300008 App.202305 4iC_2822B