Research Article | Vol. 9, No. 10 | 1 Oct 2018 | BIOMEDICAL OPTICS EXPRESS 4893
Biomedical Optics EXPRESS

Visual acuity of pseudophakic patients predicted from *in-vitro* measurements of intraocular lenses with different design

Fidel Vega,[1,*] Maria S. Millán,[1] Nuria Garzón,[2] Irene Altemir,[3,4] Francisco Poyales,[2] and Jose Manuel Larrosa[4]

[1]*Departament d'Òptica i Optometria, Universitat Politècnica de Catalunya, BarcelonaTech, Violinista Vellsolà 37, 08222 Terrassa, Spain*
[2]*IOA Madrid, Innova Ocular, Galileo 104, 28003 Madrid, Spain*
[3]*Miguel Servet University Hospital, Ophthalmology Department, Paseo Isabel La Católica, 1-3 50009 Zaragoza, Spain*
[4]*Aragon Institute for Health Research (IIS Aragón), University of Zaragoza, Edificio CIBA, Planta 0 Avda. San Juan Bosco, 1-3 50009 Zaragoza, Spain*
**fidel.vega@upc.edu*

Abstract: The optical quality of a set of IOLs (modeling set: one monofocal and two bifocals) was assessed through focus by the area under the modulation transfer function (MTFa) metric and related to the visual acuity (VA) defocus curves of pseudophakic patients implanted with said IOLs. A non-linear relationship between the MTFa and clinical VA was obtained with an asymptotic limit found to be the best VA achievable by the patients. Two mathematical fitting functions between clinical VA and MTFa were derived with high correlation coefficients ($R^2 \geq 0.85$). They were applied to the MTFa obtained from a different set of IOLs with advanced designs (trial set: one extended range of vision –ERV-, one trifocal ERV and one trifocal apodized) to predict VA versus defocus of patients implanted with these IOLs. Differences between the calculated VA and the clinical VA for both fitting models were within the standard deviation of the clinical measurements in the range of -3.00 D to 0.00 D defocus, thus proving the suitability of the MTFa metric to predict clinical VA performance of new IOL designs.

OCIS codes: (330.1070) Vision - acuity; (170.4470) Ophthalmology; (330.7335) Visual optics, refractive surgery; (330.7326) Visual optics, modeling; (170.4460) Ophthalmic optics and devices; (050.1965) Diffractive lenses.

References and links

1. A. J. Lang, V. Lakshminarayanan, and V. Portney, "Phenomenological model for interpreting the clinical significance of the in vitro optical transfer function," J. Opt. Soc. Am. A **10**(7), 1600–1610 (1993).
2. A. Felipe, F. Pastor, J. M. Artigas, A. Diez-Ajenjo, A. Gené, and J. L. Menezo, "Correlation between optics quality of multifocal intraocular lenses and visual acuity: tolerance to modulation transfer function decay," J. Cataract Refract. Surg. **36**(4), 557–562 (2010).
3. A. B. Plaza-Puche, J. L. Alió, S. MacRae, L. Zheleznyak, E. Sala, and G. Yoon, "Correlating optical bench performance with clinical defocus curves in varifocal and trifocal intraocular lenses," J. Refract. Surg. **31**(5), 300–307 (2015).
4. A. Alarcon, C. Canovas, R. Rosen, H. Weeber, L. Tsai, K. Hileman, and P. Piers, "Preclinical metrics to predict through-focus visual acuity for pseudophakic patients," Biomed. Opt. Express **7**(5), 1877–1888 (2016).
5. M. J. Kim, L. Zheleznyak, S. Macrae, H. Tchah, and G. Yoon, "Objective evaluation of through-focus optical performance of presbyopia-correcting intraocular lenses using an optical bench system," J. Cataract Refract. Surg. **37**(7), 1305–1312 (2011).
6. L. Zheleznyak, M. J. Kim, S. MacRae, and G. Yoon, "Impact of corneal aberrations on through-focus image quality of presbyopia-correcting intraocular lenses using an adaptive optics bench system," J. Cataract Refract. Surg. **38**(10), 1724–1733 (2012).
7. M. Packer, Y. R. Chu, K. L. Waltz, E. D. Donnenfeld, R. B. Wallace 3rd, K. Featherstone, P. Smith, S. S. Bentow, and N. Tarantino, "Evaluation of the aspheric Tecnis multifocal intraocular lens: One-year results from the first cohort of the Food and Drug Administration clinical trial," Am. J. Ophthalmol. **149**(4), 577–584.e1 (2010).

#334797 https://doi.org/10.1364/BOE.9.004893
Journal © 2018 Received 11 Jun 2018; revised 26 Jul 2018; accepted 3 Aug 2018; published 17 Sep 2018

Biomedical Optics EXPRESS

8. J. S. Kim, J. W. Jung, J. M. Lee, K. Y. Seo, E. K. Kim, and T. I. Kim, "Clinical outcomes following implantation of diffractive multifocal intraocular lenses with varying add powers," Am. J. Ophthalmol. **160**(4), 702–709.e1 (2015).
9. F. T. A. Kretz, M. Gerl, R. Gerl, M. Müller, G. U. Auffarth, A. Liekfeld, M. Saeed, C. Lenis, D. Smadja, N. Gabric, E. Mukrwa-Kominek, K. Qureshi, A. Hamid, J. Vasselon, and W. Strauch, "Clinical evaluation of a new pupil independent diffractive multifocal intraocular lens with a +2.75 D near addition: a European multicentre study," Br. J. Ophthalmol. **99**(12), 1655–1659 (2015).
10. Y.-S. Yoo, W.-J. Whang, Y.-S. Byun, J. J. Piao, D. Y. Kim, C.-K. Joo, and G. Yoon, "Through-focus optical bench performance of extended depth-of-focus and bifocal intraocular lenses compared to a monofocal lens," J. Refract. Surg. **34**(4), 236–243 (2018).
11. D. R. H. Breyer, H. Kaymak, T. Ax, F. T. A. Kretz, G. U. Auffarth, and P. R. Hagen, "Multifocal intraocular lenses and extended depth of focus intraocular lenses," Asia Pac. J. Ophthalmol. (Phila.) **6**(4), 339–349 (2017).
12. L. He, X. Hong, and R. Sarangapani, "Population-based simulation using image quality metrics to predict visual acuity in pseudophakic patients implanted with trifocal IOLs," Invest. Ophthalmol. Vis. Sci. **58**(8), 4209 (2017).
13. G. Cardona, F. Vega, M. A. Gil, C. Varón, J. A. Buil, and M. S. Millán, "Visual acuity and image quality in 5 diffractive intraocular lenses," Eur. J. Ophthalmol. **28**(1), 36–41 (2018).
14. Abbott Medical Optics, https://www.vision.abbott
15. H. A. Weeber, "Multi-ring lens, systems and methods for extended depth of focus," US Patent No. 2014/0168602 A1. Pub. Date: Jun 19, 2014.
16. H. A. Weeber, S. T. Meijer, and P. A. Piers, "Extending the range of vision using diffractive intraocular lens technology," J. Cataract Refract. Surg. **41**(12), 2746–2754 (2015).
17. H. A. Weeber and P. A. Piers, "Theoretical performance of intraocular lenses correcting both spherical and chromatic aberration," J. Refract. Surg. **28**(1), 48–52 (2012).
18. M. S. Millán and F. Vega, "Extended depth of focus intraocular lens: Chromatic performance," Biomed. Opt. Express **8**(9), 4294–4309 (2017).
19. D. Gatinel, C. Pagnoulle, Y. Houbrechts, and L. Gobin, "Design and qualification of a diffractive trifocal optical profile for intraocular lenses," J. Cataract Refract. Surg. **37**(11), 2060–2067 (2011).
20. V. S. Y. Biotechnology, http://www.vsybiotechnology.com
21. F. Vega, F. Alba-Bueno, and M. S. Millán, "Energy distribution between distance and near images in apodized diffractive multifocal intraocular lenses," Invest. Ophthalmol. Vis. Sci. **52**(8), 5695–5701 (2011).
22. F. Vega, F. Alba-Bueno, and M. S. Millán, "Energy efficiency of a new trifocal intraocular lens," J. Eur. Opt. Soc. **9**, 14002 (2014).
23. F. Vega, F. Alba-Bueno, M. S. Millán, C. Varón, M. A. Gil, and J. A. Buil, "Halo and Through-Focus Performance of Four Diffractive Multifocal Intraocular Lenses," Invest. Ophthalmol. Vis. Sci. **56**(6), 3967–3975 (2015).
24. International Organization for Standardization, ISO 11979–2:2014 "Ophthalmic Implants - Intraocular Lenses - Part 2: Optical Properties and Test Methods." Geneva; ISO; 2014.
25. F. Vega, M. S. Millán, and B. Wells, "Spherical lens versus aspheric artificial cornea for intraocular lens testing," Opt. Lett. **35**(10), 1539–1541 (2010).
26. A. Guirao, M. Redondo, and P. Artal, "Optical aberrations of the human cornea as a function of age," J. Opt. Soc. Am. A **17**(10), 1697–1702 (2000).
27. L. Wang, E. Dai, D. D. Koch, and A. Nathoo, "Optical aberrations of the human anterior cornea," J. Cataract Refract. Surg. **29**(8), 1514–1521 (2003).
28. M. J. Simpson, "Diffractive multifocal intraocular lens image quality," Appl. Opt. **31**(19), 3621–3626 (1992).
29. J. S. Wolffsohn, A. N. Jinabhai, A. Kingsnorth, A. L. Sheppard, S. A. Naroo, S. Shah, P. Buckhurst, L. A. Hall, and G. Young, "Exploring the optimum step size for defocus curves," J. Cataract Refract. Surg. **39**(6), 873–880 (2013).
30. L. He, M. Choi, X. Hong, and R. Sarangapani, "Correlation between clinical visual acuity and optical/visual metrics at varied defocuses in pseudophakic patients implanted with monofocal and multifocal IOLs," Invest. Ophthalmol. Vis. Sci. **56**(7), 2978 (2015).
31. P. A. Piers, D. H. Chang, A. Alarcón, C. Cánovas, D. Gatinel, and J. Loicq, "Clinically relevant interpretation of optical bench measurement of intraocular lenses," J. Refract. Surg. **33**(1), 64 (2017).
32. D. A. Rosser, S. N. Cousens, I. E. Murdoch, F. W. Fitzke, and D. A. Laidlaw, "How sensitive to clinical change are ETDRS logMAR visual acuity measurements?" Invest. Ophthalmol. Vis. Sci. **44**(8), 3278–3281 (2003).
33. A. Alarcón, C. Canovas, R. Rosen, H. Weeber, and P. Piers, "Apparatus, systems and methods for improving visual outcomes for pseudophakic patients," U.S. Patent US9823163B2. Pub Date Nov. 21, 2017.
34. E. A. Villegas, E. Alcón, and P. Artal, "Optical quality of the eye in subjects with normal and excellent visual acuity," Invest. Ophthalmol. Vis. Sci. **49**(10), 4688–4696 (2008).

1. Introduction

The optical quality of an intraocular lens (IOL) is a key parameter contributing to a patient's visual performance after cataract or refractive surgery, and has drawn the attention of increasing number of researchers in the last years (e.g., [1–4]). This investigation can help: 1) designers of intraocular lenses, to better estimate the relative effects of modifying an implant

Biomedical Optics EXPRESS

design on an average patient's vision, 2) manufacturers, to determine a more accurate control and provide more useful specifications of their ophthalmic products, and 3) surgeons, to better evaluate the implications of specific optical parameters in the IOL selection. The difficulty lies in finding imaging quality metrics derived from objective measurements on optical bench (for example, metrics based on the optical transfer function) that highly correlates with subjective quality metrics of visual performance as measured by clinical tests (for example, visual acuity and contrast sensitivity). If these highly correlated metrics were found, it would be possible to predict the relative change in the clinical outcomes from a given change in the optical component (intraocular lens) tested on optical bench for a pupil range and different alignment conditions.

Using a phenomenological approach, Lang et al. built up a model to predict the visual acuity (VA) and contrast sensitivity outcomes of clinical tests from in-vitro measurements of the modulation transfer function (MTF) taking into account a simple model of human threshold detection [1]. They computed and plotted graphs to predict VA versus defocus from through-focus MTF measurements at certain spatial frequencies and compared their theoretical results with the visual function measured clinically in pseudophakic (monofocal and bifocal) patients. Felipe et al. [2], also considered VA outcomes and MTF measurements on an optical bench (averaged in the range of 0 to 100 cycles per millimeter –approximately equivalent to 30 cycles per degree (cpd)) in their study with three different bifocal IOL designs. They searched for a mathematical relationship between VA and averaged MTF, and computed linear fits between both magnitudes from data obtained in either photopic or mesopic conditions. A maximum correlation coefficient of $R^2 = 0.91$ was reached in photopic conditions. Plaza-Puche et al. [3], found significant correlations between another image quality metric (IQM) based on cross-correlation coefficients computed from images obtained on optical bench [5, 6] and VA clinically determined using a defocus curve measured in pseudophakic patients. Their study considered three types of IOL (monofocal, refractive varifocal and trifocal) and a linear predicting model with reported $R^2 = 0.85$. Alarcon et al. [4], in their comprehensive paper proposed up to four metrics based on optical-bench data, three of them, using MTF based values integrated in a spatial frequency range, and a fourth, using the cross-correlation coefficient IQM to correlate with binocular VA clinically tested in pseudophakic patients implanted with six different IOL designs including two monofocals, three bifocals and one extended-range-of-vision (ERV), all of them from Abbott Medical Optics (Santa Ana, California).

Nonlinear fitting functions between the clinical VA and each metric (x) with the power function form $VA(x) = a \cdot x^b + c$ were derived and evaluated, with high R^2 correlation coefficients in all cases. For example, metric MTFa, defined as the area under the MTF curve from 0 to 50cpmm (equivalently, from 0 to around 15 cycles per degree in the object space), fitted with $b = -1$, reached $R^2 = 0.95$. The results led the authors to suggest that any of these metrics, as a variable of non-linear functions, could predict clinical average defocus VA curves, thus becoming *preclinical metrics*. Since various IOL designs were used in the experiment, including refractive and diffractive designs, different materials, amounts of spherical aberration, and add powers, the authors suggested that the correlations found in their study might be applicable for a wide range of IOL designs, although they did not report further verifications.

In this work, we verify that the function that fits a MTF based optical-bench metric (MTFa) to clinical VA data of pseudophakic patients implanted with a set of IOLs (modeling set) can also be used to predict the clinical VA outcomes of pseudophakic patients implanted with IOLs of very different design, i.e. not included in the modeling set. To the best of our knowledge, such a kind of verification has not been reported yet. For that purpose, we consider two sets of IOLs: the first one –modeling set- consists of three widely studied IOLs (one monofocal and two bifocals) [7–10] and the second one –trial set- consists of three more IOLs of advanced design (one ERV, one trifocal ERV and one trifocal apodized) [11]. We

Biomedical Optics EXPRESS

compare through-focus MTFa curves obtained using an eye-model on optical bench with VA defocus curves obtained clinically with patients following a pseudophakic implant with some of the six IOLs. We have enlarged the through-focus range to cover from + 3.0 D to −5.0 D in comparison with the referred works [2–4, 12]. In a prior study with six differently featured IOLs, we obtained that, beyond a certain level of optical quality established by a threshold value of the MTFa metric, any further increase in MTFa did not produce any noticeable improvement in VA [13]. Therefore, in this work, we hypothesize an asymptotic limit in the VA achievable by patients implanted with IOL designs with exceedingly large MTFa and refine the non-linear function that fits optical-bench with clinical data. The results are further discussed and compared with the power function approach proposed by Alarcon et al. [4].

2. Material and methods

2.1 Intraocular lenses

Six different IOLs, all of them with optical power for distance vision of 20 D, were analyzed in vitro in our test bench: a monofocal ZCB00, two bifocals ZLB00 and ZMB00, the ERV Symfony ZXR00 (all of them Tecnis, Abbott Medical Optics, Abbott Park, IL), the trifocal ERV Acriva^{UD} Reviol Tri-ED (VSY Biotechnology, Istanbul, Turkey) and the trifocal apodized FineVision (POD F) (Physiol, Lieje, Belgium). These IOLs were grouped in two sets: the modeling set, with the monofocal ZCB00 and the two bifocals (ZLB00 and ZMB00), and the trial set, with the ERV Symfony ZXR00 and the two trifocals (Acriva^{UD} Reviol Tri-ED and FineVision). IOL specifications are listed in Table 1.

Table 1. Optical data of the IOLs.

	Modeling set			Trial set		
	ZCB00[a]	ZLB00[a]	ZMB00[a]	Symfony[a] ZXR00	FineVision[b]	Acriva^{UD} Reviol Tri-ED[c]
Material	Hydropho[d] Acrylic	Hydropho[d] Acrylic	Hydropho[d] Acrylic	Hydropho[d] Acrylic	Hydrophilic Acrylic	Acrylic with hydrophobic surface
Refractive index n	1.47	1.47	1.47	1.47	1.46	1.46
Aspheric surface	Anterior	Anterior	Anterior	Anterior	Posterior	Anterior
SA = c[4,0] (μm)[e]	-0.27	–0.27	–0.27	–0.27	–0.11	–0.165
Diffractive design	NA[f]	Full-aperture Posterior	Full-aperture Posterior	Pupil-dependent Posterior	Pupil-dependent Anterior	Pupil-dependent Anterior
Base Power (D)	20	20	20	20	20	20
Add Power (D)	NA[f]	+ 3.25	+ 4.0	+ 1.75	+ 1.75, + 3.50	+ 1.5, + 3.0

[a] Tecnis (Abbot Medical Optics Inc.). [b] FineVision POD F (Physiol, Lieje, Belgium). [c] Acriva^{UD} Reviol Tri-ED (VSY Biotechnology, Istanbul, Turkey). [d] Hydrophobic. [e] 6mm pupil. [f] NA, not applicable

All four Tecnis IOLs shared the same material and had the same aspheric design of the refractive base lens [14]. The two bifocals (ZLB00 and ZMB00) had a hybrid refractive-diffractive design intended to produce a balanced and pupil independent distribution of energy (41%) between distance and near foci. The Symfony ZXR00 IOL is designed with a proprietary method [15] for providing ERV [16] with combined correction of both, spherical and longitudinal chromatic aberrations with additional contrast sensitivity enhancement and reduction of photic phenomena [17]. Its design is pupil dependent, so the energy distribution benefits the distance focus for increasing pupils. We have recently reported a detailed analysis of the basis of focus extension and chromatic performance of this lens [18]. More specifically, we showed that under monochromatic green illumination, the design of the Symfony lens

Biomedical Optics EXPRESS

corresponds to a bifocal IOL with low addition (+ 1.75 D) that, unlike conventional diffractive bifocal IOLs, uses the first and second diffractive orders for the far and near foci, respectively.

Regarding the trifocal FineVision lens, it has an apodized diffractive profile in its anterior surface, which means than the step height of the diffractive rings gradually decreases toward the periphery, resulting in a continuous change of the light energy distribution among the three primary foci. Indeed, the amount of energy directed to far-vision focus is superior to that directed for intermediate and near-vision foci (far 42%, intermediate 15%, near 29% under photopic condition with a 3 mm pupil diameter) [19].

Finally, the AcrivaUD Reviol Tri-ED has a one-piece diffractive trifocal ERV design according to their technical specifications [20]. A trifocal and ERV combined performance is created by changing height, width, interval, and number of diffractive rings, with the entire aperture covered by 25 rings. Light energy, under photopic conditions, is distributed among the three foci (far 40%, intermediate 30% and near 30%, respectively).

2.2 Optical test bench and MTFa quality metric

The test bench with the model eye used to measure the optical performance of the IOLs *in vitro* is schematically shown in Fig. 1 and has been described in detail elsewhere [13, 21, 22]. It mainly consists of three parts: the illumination system, the model eye, and the image acquisition system.

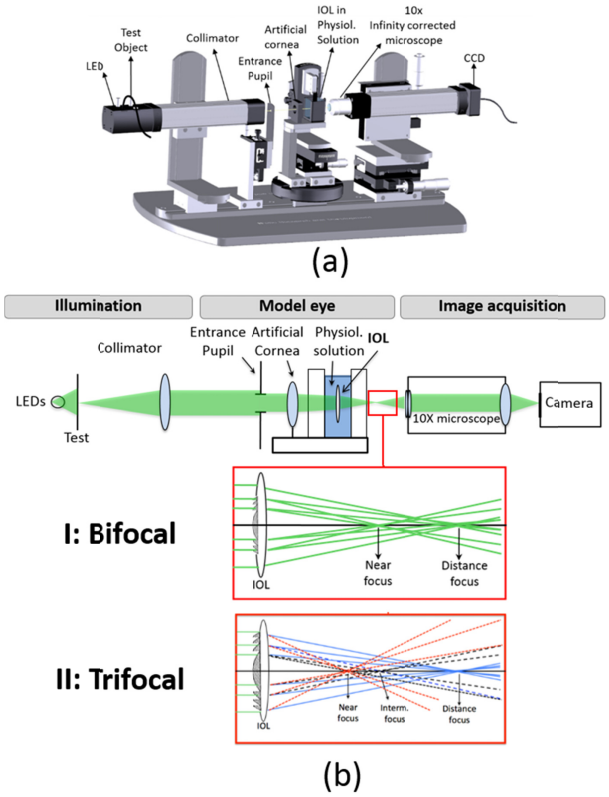

Fig. 1. - Optical setup used for *in vitro* assessment of IOLs. (a) General view. (b) Scheme of the optical setup. Inset I: bifocal diffractive IOL; inset II: trifocal diffractive IOL. LED = light-emitting diode.

Biomedical Optics EXPRESS

The light source of the illumination system was a green light emitting diode (LED) (Thorlabs GmbH, Munich, Germany) with emission centered at 530 nm and with a full-width half-maximum spectral band width of 32 nm, which illuminated a test object located at the front focal plane of a collimator (200 mm focal length). The test object was a four-slit pattern, two along horizontal axis X and two along vertical axis Y, for MTF measurement (Fig. 2) [23]. The width of the slits were 10 μm. The collimated beam illuminated the model eye, which was formed by an artificial cornea and a wet cell where the IOL under test was placed. The model eye followed the recommendations of the International Standard Organization 11979-2: 2014 [24] regarding the use of an aberration-inducing artificial cornea for evaluation of aspheric IOLs. In particular, our cornea induced an amount of spherical aberration (SA) at the IOL plane of + 0.27 μm (for a 6.0 mm pupil) [25], which is similar to the average human cornea [26, 27].

An iris diaphragm, placed in front of the artificial cornea was used to control the lens aperture and hence, the level of corneal SA of the wavefront that impinged upon the tested IOL. The pupil diameters mentioned in this work are referred to the IOL plane [21, 22]. All the results in the test bench were obtained with a pupil of 3.0 mm.

Finally, the image acquisition system was composed of an infinity corrected microscope with an 8-bit CCD camera, mounted in a high precision, three-axis translation holder. The microscope objective was a 10X Olympus Plan Achromat designed for high-quality imaging applications due to its diffraction limited performance across the entire visible spectrum. The image acquisition system (microscope and camera) was diffraction limited with a cutoff frequency of 675 cycles/mm.

To obtain the through focus MTF of the IOLs, the four-slit object was imaged by the model eye, with the IOL under study immersed in the wet cell, and the space image was scanned with the acquisition system between −5.0D to + 3.0D in 0.10D steps [23]. According to the clinical convention, negative dioptric values correspond to near target vergences. To reduce electronic noise, each image was the result of averaging eight frames at a time. The optical quality of these images was assessed by means of the MTFa metric [4] as illustrated in Fig. 2. To calculate this image quality metric at each defocus position, we computed the MTF of each slit from the modulus of the Fourier transform of the line spread function as reported in Ref [28].

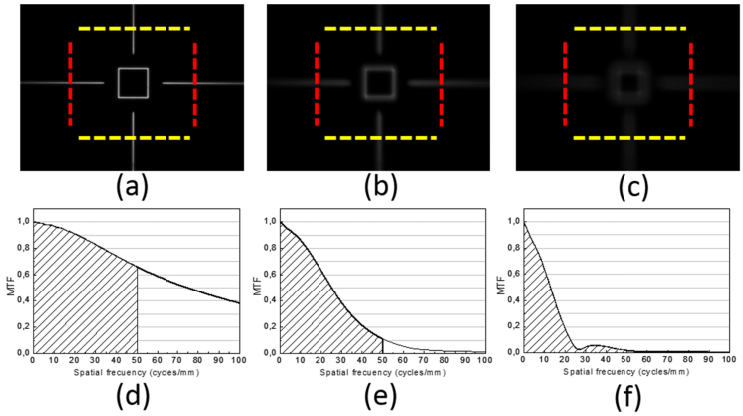

Fig. 2. Example to illustrate the relationship between image quality and the area under the MTF (MTFa) metric. The images (a, b, c) of the four slit object were recorded at defocus 0.00 D (a), −0.50 D (b) and −1.00 D (c) with the monofocal ZCB00 IOL placed in the model eye. The MTFs derived from these images are shown in (d), (e) and (f) respectively and were obtained from the average of four MTFs: two along the X axis (yellow dashed lines) and two along the Y axis (red dashed lines). The MTFa at each defocus position is the shaded area below the MTF curves calculated from 0 up to 50 cycles/mm in (d-f).

Biomedical Optics EXPRESS

Once the MTF of the four slit images –two horizontal and two vertical (Figs. 2(a-c))- were computed and averaged, the MTFa was calculated by integrating the resulting average MTF curve from 0 to 50 cycles/mm (Figs. 2(d-f)) as reported elsewhere [4].

2.2 Clinical data

The clinical data for this study were obtained from 279 eyes from 159 patients recruited for two clinical trials carried out at two ophthalmology centers (Table 2). Both studies were prospective, consecutive and non-randomized and followed the tenants of the declaration of Helsinki. The patients underwent bilateral and symmetric cataract surgery followed by IOL implantation into the capsular bag. Previously, they had been fully informed about the study and signed a consent form. The local ethics committee of the corresponding ophthalmology center approved each clinical trial.

Eligible patients for the study were aged between 50 and 75, with presence of bilateral cataracts and no comorbidities. Specific inclusion criteria were regular corneal astigmatism of ≤1.00D, VA higher than 0.6 in logMAR scale, and IOL power between + 17.00 D and + 27.00 D. For the multifocal lenses, other inclusion criteria were the desire for spectacle independence after surgery with realistic expectations, and availability and willingness to comply with examination procedures.

Key exclusion criteria were irregular astigmatism, ocular comorbidities, history of ocular trauma or prior ocular surgery including refractive procedures, acute or chronic disease or illness that would increase risk or confound study results, such as age-related macular degeneration, glaucoma or corneal disorder, capsule or zonular abnormalities.

Table 2. Clinical data.

Setting	IOL implanted	Number of patients
IOA Madrid, Innova Ocular, Madrid (Spain)	ZLB00 (bifocal)	15
	FineVision (trifocal apodized)	21
	Acriva^{UD} Reviol TRI-ED (trifocal ERV)	15
Miguel Servet University Hospital, Zaragoza (Spain)	ZCB00 (monofocal)	41
	ZMB00 (bifocal)	41
	Symfony ZXR00 (ERV)	26

All patients underwent the same preoperative protocol that included optical biometry with IOLMaster 500 (Carl Zeiss AG, Oberkochen, Germany), Pentacam topography (Oculus, Wetzlar, Germany), intraocular pressure with Goldmann applanation tonometer, slit lamp biomicroscopy evaluation, optical coherence tomography with Cirrus OCT (Carl Zeiss, Dublin, California, USA) and fundus examination.

In all cases, the lenses were calculated for emmetropia. All surgical procedures were performed under topical anesthesia. For phacoemulsification, a 2.2 mm clear corneal incision was made. Next, a continuous curvilinear capsulorhexis measuring approximately 5.5 mm in diameter was created. Two ophthalmic viscosurgical devices (OVD) were used, cohesive Healon (Abbott Laboratories Inc. Abbott Park, IL, USA) and the dispersive Amvisc (Bausch & Lomb, Inc., Rochester NY). All lenses were implanted through a 2.2 mm incision using an injector to facilitate implantation. All traces of OVD were removed. No patient included in the study suffered any intraoperative or postoperative complication, and all were operated on according to the established protocol.

Monocular defocus VA curves between −5.00 D and + 3.00 D, with the patients having their best distance correction, were measured in logMAR scale during the last postoperative follow up. The measurements were carried out using the 100% contrast Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 m under photopic conditions and with natural eye pupil. Following the procedure described by Wolffsohn et al. in [29], patients were first

Biomedical Optics EXPRESS

defocused to −5.00 D, and defocus was then decreased up to 0.00 D defocus by adding spherical positive lenses in 0.5 D increments. Patients were subsequently defocused to + 3.00 D and the VA curve was completed by measuring between + 3.00 D and 0.00 D by adding spherical negative lenses in 0.5 D steps. To avoid learning effects, three different copies of the ETDRS chart were alternated during the test.

3. Results

3.1 Mathematical relationship between VA and MTFa using the IOL modeling set

Figure 3 depicts experimental results obtained with IOLs of the modeling set (Table 1): Figs. 3(a, b) show the mean clinical values of VA in the range −5.00 D to + 3.00 D measured in pseudophakic patients and Figs. 3(c, d) the through focus MTFa, obtained *in-vitro* in the model eye under green illumination. For the sake of comparison, all four figures (a-d) include results of monofocal ZCB00 and one bifocal, either ZLB00 (+ 3.25D) in Figs. 3(a, c) or ZMB00 (+ 4.0D) in Figs. 3(b, d).

The three groups of pseudophakic patients had their best VA at 0.00 D defocus (distance vision) with values very close to 0.00 logMAR (−0.03 ± 0.08 ZCB00, −0.01 ± 0.06 ZLB00 and −0.02 ± 0.07 ZMB00, respectively). As expected, while the monofocal group shows a Λ-shaped defocus curve, with monotonous decay of VA with increasing negative defocus, both bifocal groups exhibit M-shaped defocus curves, with additional VA peaks at near vergences of −2.50 D for ZLB00 (Fig. 3(a)) and −3.00 D for ZMB00 (Fig. 3(b)). The VA values at these peaks of near vision were slightly worse (0.10 ± 0.06 for ZLB00 and 0.06 ± 0.08 for ZMA00) than the corresponding VA values reached at distance vision (0.00 D defocus). The position of the near vision peaks in the defocus curves matched the IOL addition powers at the spectacle plane.

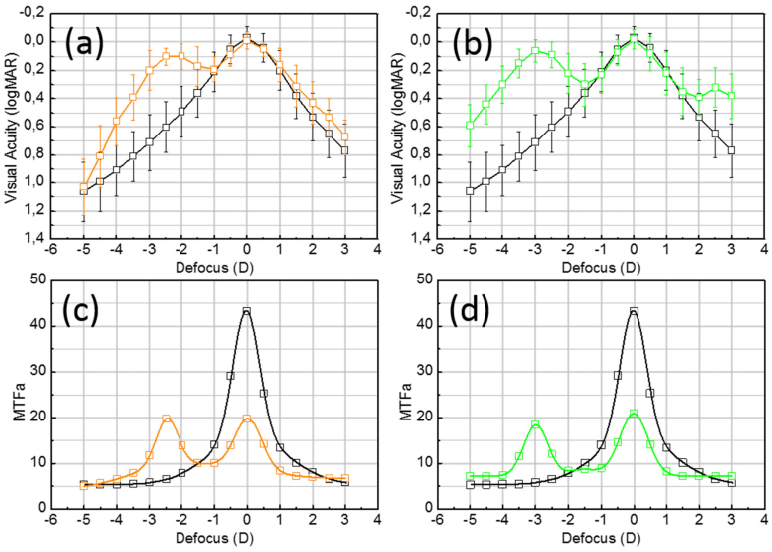

Fig. 3. Clinical Visual acuity (mean ± standard deviation) (a, b) and MTFa (c, d) versus defocus (at spectacle plane) obtained with monofocal ZCB00 (black line) and bifocals ZLB00 (+ 3.25 D) (orange line) and ZMB00 (+ 4.0 D) (green line). The squares in (c) and (d) are the MTFa values at the defocus positions for which the clinical VA is measured.

The through focus MTFa curves of Figs. 3(c, d) have shapes that qualitatively resemble those of the VA defocus curves of Figs. 3(a, b). As such, monofocal ZCB00 has a single peak with the highest MTFa value, and thus, the best optical quality at 0.00 D defocus with monotonous decay at either side. Bifocals ZLB00 and ZMB00 have a MTFa peak at 0.00 D

Biomedical Optics EXPRESS

defocus as well but, additionally, they have a second peak at a near vergence corresponding to the IOL addition power at the spectacle plane (–2.50 D ZLB00 and –3.00 D ZMB00, respectively). Note that, in the case of the bifocal IOLs, the MTFa values at the two (far and near) peaks are quite balanced (around 20). These results agree well with both bifocal designs, intended for a balanced performance of their two foci [10].

It is worth highlighting the large differences found in the value of the MTFa at 0.00 defocus, between the monofocal and the two counterpart bifocal IOLs ($MTFa_{ZCB00}$ = 43.3 versus $MTFa_{ZLB00}$ = 19.8 and $MTFa_{ZMB00}$ = 21 in Figs. 3(c, d)), the later meaning that the monofocal IOL has a considerably higher in vitro optical quality around this 0.00 D defocus position. This great difference in the MTFa peak values does not translate to the VA defocus curves of Figs. 3(a, b), where the VA scores at distance vision are practically indistinguishable for patients implanted with monofocal or bifocal IOLs. This result is consistent with evidence already reported in references [8, 9, 13].

The results shown in Fig. 3 allow us to obtain, for a given IOL, a pair of values (MTFa,VA) at each defocus position and hence, to study the relationship between both parameters in the range of –5.00 D to + 3.00 D. Since we took a measurement every 0.50 D, we were able to obtain 17 pairs of (MTFa,VA) values for each lens. The results, plotted in Fig. 4, include the values found with the three IOLs of the modeling set: monofocal ZCB00 and bifocals ZLB00, ZMB00 and show a non-linear relationship between clinical VA and in-vitro MTFa. To help with the interpretation of this Fig. 4 we have highlighted the (MTFa,VA) pairs at the 0.00 D defocus (i.e., where the best VA and largest MTFa concurs) in the case of the monofocal ZCB00 (*) and the bifocals ZLB00 and ZMB00 (**).

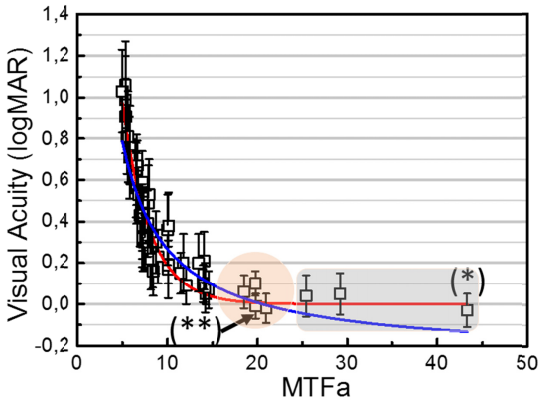

Fig. 4. Relationship between clinical Visual Acuity (mean ± standard deviation) and MTFa obtained with the IOLs of the set of modeling: monofocal ZCB00 and bifocals ZLB00 (+ 3.25 D) and ZMB00 (+ 4.0 D). Open squares are experimental results and each of them represents a pair (MTFa,VA) for a particular IOL model and defocus position. The pair (MTFa,VA) at 0.00 D defocus of the monofocal ZCB00 and bifocals ZLB00 and ZMB00 are indicated by (*) and (**) respectively. Solid blue line: function fitted with Eq. (1) [4]. Solid red line: exponential decay fitted with Eq. (2).

Two more (MTFa,VA) pairs, corresponding to the MTFa and VA peaks of the bifocals at near (defocus of –2.50 D and –3.00 D for ZLB00 and ZMB00 respectively), appear grouped with those two points of distance vision marked with (**). These four (MTFa,VA) pairs grouped together in the pink region of Fig. 4 evidence good clinical VA outcomes, as it was already pointed out in Figs. 3(a, b). Moreover, such a good VA grade (about 0.0 logMAR) is also shared with three more (MTFa,VA) pairs (grey region) that correspond to the monofocal ZCB00 at defocus levels of 0.00 D and ± 0.50 D. All these points gathered in the pink and

Biomedical Optics EXPRESS

grey regions of Fig. 4 define a limit for the achievable VA despite increasing optical imaging quality.

The many experimental points (51 points in total) represented in Fig. 4 demonstrate a relationship between clinical VA and in vitro MTFa that associates, in general, larger values of MTFa (or equivalently, better optical quality) with better clinical VA scores (i.e. lower logMAR values). This relationship can no longer be represented by a linear function as it has been formerly done from fewer points [2]. Moreover, for MTFa values over certain threshold (set somehow arbitrarily around 20 in Fig. 4), changes in VA are barely noticeable from a VA value that remains almost constant and very close to 0.0 logMAR.

The non-linear relationship found between clinical VA and MTFa in Fig. 4 led us to try different functions to fit the experimental data. The first one was the power function proposed by Alarcón et al. [4], given by:

$$VA\left(MTF_a\right) = a\left(MTF_a\right)^{-1} + c, \tag{1}$$

The best fit of our experimental data with Eq. (1) occurs with c = -0.25 ± 0.03 logMAR and a = 5.17 ± 0.32 (R^2 = 0.845). As shown in Fig. 4 (solid blue line), this function works reasonably well for MTFa values up to approximately 20 but tends to overestimate calculated VA for MTFa values larger than 20. As such, in the case of the monofocal ZCB00, with a measured MTFa of 43.3 at 0.00 D defocus, Eq. (1) would result in a VA value of –0.13 logMAR when, clinically, the assessed VA was only –0.03 ± 0.08 logMAR at this defocus position.

This fact can be included in the model by acknowledging that parameter c in Eq. (1) is the asymptotic value of VA for large MTFa, and thus it would represent the potentially best VA achievable with an IOL design that showed exceedingly large MTFa (or equivalently, exceptional optical quality) [13]. This reasoning led us to try another non-linear fitting function that could provide an asymptotic value for calculated better VAs, closer to the experimental results found in our clinical trials. From our clinical data (Fig. 4), we set such asymptotic VA value at 0.0 logMAR. The function that fulfilled this restriction and had the highest R^2 correlation coefficient, i.e. showed the best fidelity between experimental and fitted results, was an exponential decay function of the form:

$$VA\left(MTF_a\right) = A\exp\left\{-\frac{MTF_a}{B}\right\} + c, \tag{2}$$

with calculated free fit parameters A = 5.06 ± 1.32, B = 3.03 ± 0.35 and c = 0.00 logMAR, the latter having a standard deviation of zero to the second significant decimal place (e.g., 0.00). The correlation coefficient R^2 = 0.903 of the resulting function is higher than using Eq. (1). The new exponential function, plotted in Fig. 4 (solid red line), shows that, for values of the MTFa ≥20, the exponential term in Eq. (2) becomes negligibly small (<0.007 logMAR) and the calculated VA would tend to the asymptotic value c = 0.00 logMAR, in closer agreement to the clinical VA values.

3.2 Testing the model with the IOL trial set

Figure 5 shows the through focus MTFa curves measured *in-vitro* for each IOL of the trial set: (a) ERV Symfony, (b) trifocal ERV Acriva^{UD} Reviol Tri-ED, and (c) trifocal apodized FineVision IOLs.

Biomedical Optics EXPRESS

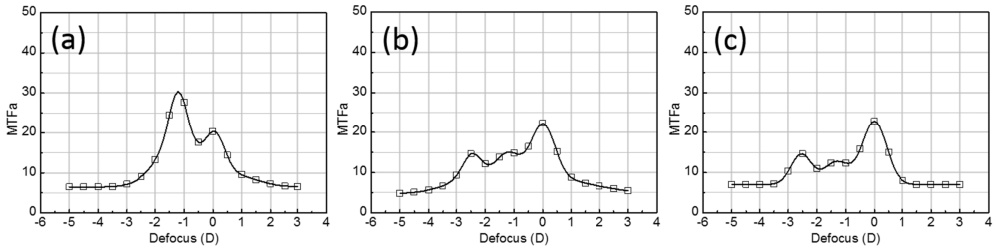

Fig. 5. MTFa versus defocus obtained with the IOLs of the set of trial: ERV Symfony (a), trifocal Acriva^{UD} Reviol Tri-ED (b) and trifocal apodized FineVision (c). Squares in (a), (b) and (c) are the MTFa values at the defocus positions used to preclinical estimate VA in these IOLs.

By using the MTFa values showed in Fig. 5 and the two fitting models (Eqs. (1) and (2)), we have estimated the VA defocus curve for each IOL of the trial set. Figure 6 depicts the calculated VA values and they are compared to clinical VA measured in patients implanted with these IOLs.

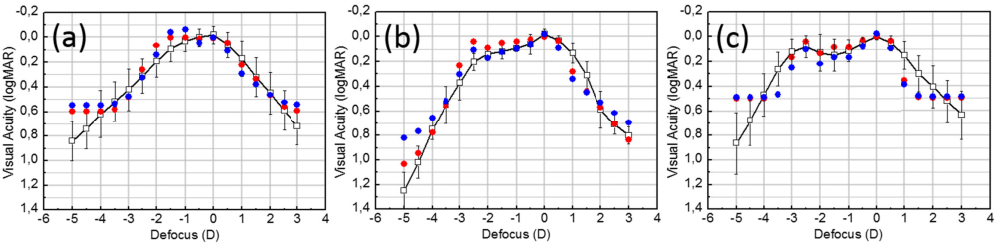

Fig. 6. Clinical Visual Acuity measurements (mean ± standard deviation) (open squares on black solid line) and calculated Visual Acuity estimates with Eq. (1) (solid blue circles) and Eq. (2) (solid red circles) versus defocus, obtained with the IOLs of the set of trial: (a) ERV Symfony, (b) trifocal Acriva^{UD} Reviol Tri-ED, and (c) trifocal apodized FineVision.

As shown in Fig. 6, both fitting equations lead to similar VA estimates, which are in very good agreement, in general, with the clinical VA grades for defocus comprised within the −3.00 D to 0.00 D range. Weaker agreement occurs for positive and negative defocus extremes. The error in the calculated VA with the three IOLs (ERV Symfony, trifocal ERV Acriva Reviol and trifocal FineVision) comes from the errors of the fitting parameters in Eq. (1) and (2) and the experimental error of the MTFa. The latter was around 1% in the defocus range of clinical interest (−3.0D to 0.0D), and increased up to a maximum of 6% for more extreme positive and negative defocus. With these values, one can estimate an error for the calculated VA equal or less than 0.05 logMAR in the −3.0D to 0.0D defocus range (where the SD of the clinical VA of the three IOLs is typically between 0.03 to 0.17 logMAR) while it increases up to around 0.1 logMAR for larger defocus (where the SD of the clinical VA oscillates between 0.19 and 0.25 logMAR).

Figure 7 shows the differences between the clinical VA and the calculated VA at the studied defocus positions for either fitting function based on Eq. (1) or Eq. (2). This figure allows us to compare these differences and realize that most of them are within the standard deviation of the clinical VA grades at every defocus position.

Biomedical Optics EXPRESS

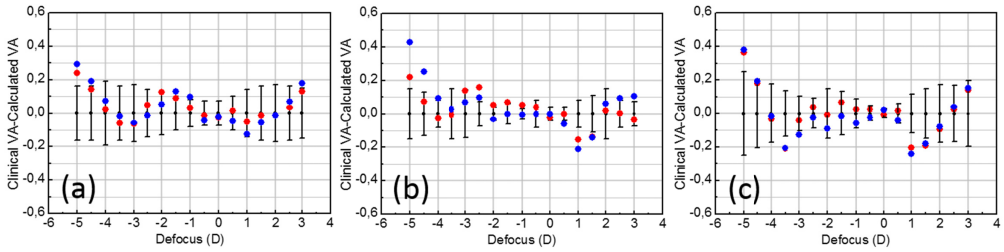

Fig. 7. Differences, at each defocus position, between the mean clinical VA and the calculated VA estimate with either Eq. (1) (solid blue circles) or Eq. (2) (solid red circles) obtained with the IOLs of the set of trial: (a) ERV Symfony, (b) trifocal ERV Acriva^{UD} Reviol Tri-ED, and (c) trifocal apodized FineVision. The error bars are the standard deviation of the clinical VA grades at every defocus position (from Fig. 6).

3. Discussion

In this study, we have verified that an optical-bench metric based on in-vitro measurement of MTF using a model eye, more specifically the MTFa, provides a good preclinical estimation of mean VA at different defocus levels in pseudophakic patients. We have covered an enlarged through-focus segment ranging from + 3.00 D to −5.00 D with 0.50 D steps. In agreement with Alarcon et al. [4], we find that better VA correlates with increased MTFa. More generally, improved MTF-based and IQM metrics correlate with improved VA [1–3, 13]. Interestingly, such relationship was reported when dealing with image quality metrics obtained with either green [2, 13, 30], or white light [1, 3, 4], but in all cases they included multiple spatial frequencies. This has been emphasized as a key aspect to accurately predict clinical performance from image quality metrics obtained in model eyes implemented in optical bench [4, 31]. Furthermore, our results have put into evidence that the relationship between clinical VA and MTFa cannot be thought as linear (Fig. 4).We have inferred for the three IOLs (modeling set: monofocal ZCB00 and bifocals ZLB00 and ZMB00) an exponential function able to predict clinical VA grades from *in-vitro* MTFa measurement at a given defocus position. Unlike the work reported by Alarcon et al [4], we have verified the model of preclinical VA estimation in patients implanted with IOLs of the trial set (ERV Symfony ZXR00, trifocal ERV Acriva^{UD} Reviol Tri-ED and trifocal apodized FineVision). We have considered two non-linear functions in a separate verification process: a power function previously proposed in Ref [4]. and an exponential decay function derived by us in this work. We remark that, despite the variety of IOL designs covered by both separate studies (monofocals, bifocals, trifocals, and ERV) and the differences concerning (their/our) experimental conditions: (white/green) illumination for *in-vitro* testing, (three/two) clinical trials, (binocular/monocular) assessment, [0.0 to −3.0D]/[+ 3.0D to −5.0D] defocus range, (same/different) IOL manufacturer, (six/three) IOLs for the modeling set, and (none/three) IOLs for the trial set, the results reached by both mathematical approaches are close. This is a key result that confirms a positive verification of the model and reinforces MTFa as a suitable preclinical metric for predicting average VA estimates in pseudophakic patients.

Taking the MTFa metric as variable, the function that expresses mathematically the variable dependence of VA estimates has been also an issue in former [4, 12] and the current study. To disclose the non-linear link between both magnitudes, the inclusion of the monofocal IOL in the study and the analysis of its results has proven to be essential because it considerably extends the range of good imaging quality, with larger values of MTFa metric (grey shaded region of Fig. 4), without producing any noticeable increase in best VA in comparison to the bifocal designs (pink shade region of Fig. 4). As shown in Fig. 3, the monofocal IOL has a MTFa of 43.3 at 0.00 D defocus (i.e., distance vision) and MTFa >25 at ± 0.50 D defocus positions, which are larger than the best MTFa values of its counterpart bifocals ($MTFa_{ZLB00}$ = 19.8 and $MTFa_{ZMB00}$ = 21). However, the clinical VA outcomes at

Biomedical Optics EXPRESS

distance vision of the three groups are equally good (Figs. 3(a) and 3(b)), with mean values just slightly below 0.00 logMAR (–0.03 ± 0.08 ZCB00, –0.01 ± 0.06 ZLB00 and –0.02 ± 0.07 ZMB00) and so, very close to the clinical VA outcomes at near vision of those groups implanted with the bifocals, with mean values just slightly over 0.00 logMAR (0.10 ± 0.06 ZLB00 and 0.06 ± 0.08 ZMB00). We recall that differences among the lenses of less than 0.1 logMAR are too small to be considered clinically significant [32]. These results are consistent with those reported in our preliminary study on the issue [13]. In comparison with the current work, for instance, Felipe et al. [2] only considered bifocal IOLs (one refractive and two diffractive) at no more than three defocus positions each (far, intermediate and near), which effectively limited the range of accessible MTFa values. From their shorter number of samples and range, they inferred a linear correlation between clinical VA and MTFa values.

Interestingly, Plaza-Puche et al. [3] included a monofocal IOL (AcrySof SA60AT) in addition to two multifocal IOLs (a varifocal Lentis Mplus and a diffractive trifocal FineVision) in their study about the correlation of clinical VA with the in-vitro IQM for defocus levels ranging from –4.00 D to + 1.00 D. Similarly to our findings concerning MTFa, they found that the monofocal IOL had better IQM at 0.00 D defocus than the varifocal and trifocal IOLs ($IQM_{monofocal}$ = 0.92 versus $IQM_{varifocal}$ = 0.81 and $IQM_{trifocal}$ = 0.80), but the clinical VA at distance vision of the patients of the three groups was very close to 0.00 logMAR with no statistical differences among them (monofocal 0.01 ± 0.02 logMAR, varifocal 0.00 ± 0.04 logMAR, and trifocal 0.04 ± 0.05 logMAR). As a consequence, the linear model they used to fit their VA and IQM results for all three IOLs together ($VA = -2.473 \cdot IQM + 2.077$), though reaching high correlation coefficient (R^2_{IQM} = 0.853), shows the larger departure from the clinical VA precisely in the case of the monofocal IOL at 0.00 D defocus (figure 3D of Ref [3].). Certainly, a clinical average VA = 0.01 ± 0.02 logMAR was obtained in the monofocal group of patients unlike the exceedingly good VA = –0.20 logMAR predicted by their linear model.

In the work of Alarcón et al. [4], they consider instead a non-linear relationship between clinical VA and MTFa, based on a power function of the form $VA = a \cdot (MTF_a)^{-l} + c$ (Eq. (1), which fitted fairly well their experimental results (R^2 = 0,951) obtained from six different IOLs tested in the –3.00 D to 0.00 D defocus range. They determined an asymptotic c parameter of –0.21 logMAR [33], which is indeed quite close to the value derived from our measurements (c = –0.25 ± 0.03 logMAR) when fitting our results with Eq. (1). However, in the range of the largest MTFa values (MTFa greater than about 20) the fit based on Eq. (1) tends to predict an improvement of VA from 0.00 logMAR when MTFa = 20, to –0.13 logMAR for MTFa = 43 (see Fig. 4 blue line), which does not represent properly what we found experimentally. Thus, the best clinical VA values with either the monofocal ZCB00 or bifocal ZLB00 and ZMB00 IOLs are nearly constant and do not go significantly below 0.00 logMAR. It can be then concluded that beyond a certain level of optical quality or, equivalently, beyond an MTFa threshold, any further increase in the value of the MTFa metric will not be accompanied by any detectable improvement in the average VA of the patients. One can hypothesize that other ocular, optical and neuro-psychophysical factors may be playing a role to prevent further increase in VA, but it is difficult to assure which ones and to which extent are the most significant [34].

Better fitting to our clinical results with the three IOLs of the modeling set (R^2 = 0.903) occurs with the non-linear approach based on the exponential function $VA = A \cdot exp(-MTF_a/B) + c$ (Eq. (2), which predicts that, for MTFa ≥20, the VA tend to an asymptotic value (or, equivalently, to a potentially best achievable VA) of c = 0.00 logMAR as experimentally observed and shown in Fig. 4. For MTFa < 20, both fitting expressions (Eq. (1) and Eq. (2)) are close (Fig. 4) and then, they predict similar VA results. This statement can be confirmed by calculating the VA versus defocus, from MTFa measurements in three IOLs of advanced design (ERV Symfony, trifocal ERV AcrivaUD Reviol Tri-ED, and trifocal apodized

Biomedical Optics EXPRESS

FineVision). For these IOLs, belonging to the trial set, most of the through focus MTFa values were below 20. As shown in Fig. 6, and for the three IOLs, both approaches lead to similar predicted VAs.

More relevant to a patient's functional range of vision, the predicted VA was in good agreement with clinical VA (Fig. 6) in the range between −3.00 D and 0.00 D, replicating the particular shape of the clinical defocus curves; e.g., from M-shape of the trifocal design (Fig. 6(c)) to a smoother mode for ERV designs (Fig. 6(a) and. 6(b)). The differences between clinical and predicted VA are mostly within the standard deviation error of the clinical measurements (Fig. 7). Such agreement extends to more extreme positive and negative defocus regions for IOL designs with varying MTFa (not constant) in such extreme defocus regions: for example, (–4.0 D to + 2.5 D) for ERV design ZXR00 in (Figs. 5a and 6(a)), (–4.50 D to + 3.00 D) for trifocal ERV Acriva Reviol TRI-ED in (Figs. 5b and 6(b)), and (–3.00 D to + 0.50 D) for trifocal FineVision in (Figs. 5c and 6(c)). Outside the referred defocus intervals the quality of the images from where the MTFa was calculated is poor and as a consequence, MTFa values are always small and nearly constant, thus leading to poorer predictability and larger differences between clinical and calculated VA, particularly in the case of the trifocal FineVision.

4. Conclusions

Clinical VA defocus curves of pseudophakic patients can be predicted from imaging quality assessments of monofocal and bifocal IOLs, tested *in vitro* in a model eye using the MTFa metric and through focus evaluation. The estimation of achievable VA, as non-linear function of variable MTFa, shows limiting behavior for IOLs with larger MTFa values, i.e. lenses with higher imaging quality. As a consequence, beyond certain MTFa threshold, VA tends asymptotically to a given value and any further increase in the imaging quality of an IOL does not translate into VA improvement.

We have verified that the function that fits optical-bench MTFa to clinical VA data of pseudophakic patients implanted with a set of IOLs (modeling set) can also be used to predict the clinical VA outcomes of patients implanted with other IOLs, not included in the set. This has been proven for a modeling set consisting of one monofocal and two bifocal IOLs, and for a trial set consisting of IOLs of advanced design (ERV and trifocals).

Funding

Spanish Ministerio de Economía y Competitividad y Fondos FEDER (DPI2016-76019-R).

Disclosures

The authors declare that there are no conflicts of interest related to this article.