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Ray-Tracing Transepithelial Excimer Laser Central Corneal Remodeling Plus Pachymetry-Guided Accelerated Corneal Crosslinking for Keratoconus

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Purpose: The aim of this study was to report the 12 to 96 months results of a tissue-preservation algorithm based on ray-tracing-guided transepithelial excimer laser central corneal ablation (RT t-PRK) combined with individualized pachymetry-guided accelerated crosslinking (M nomogram ACXL) in young adult patients with stable keratoconus (KC).

Methods: This was a prospective interventional study including 38 eyes of 38 young adult patients (stage II KC) with a mean age of 35 years (range 26–46 years) who underwent simultaneous RT with t-PRK plus pachymetry-based ACXL in the worst eye. The treatments were performed using the iViS Suite iRES Excimer Laser (Ligi, Taranto, Italy). Ray-tracing–guided treatments were planned using the customized interactive programmed transepithelial ablation (CIPTA) 2 web software and diagnostic data were assessed by the Precisio 2 tomographer (Ligi, Taranto, Italy) and Sirius tomographer (C.S.O., Florence, Italy). The main outcome measures included uncorrected distance visual acuity, best spectacle–corrected visual acuity, Kmax, high-order aberrations, minimum corneal thickness, and posterior elevation, with a mean follow-up of 52 months (range 12–96 m).

Results: The mean UDVA improved + 3.5 ±1.28 Snellen lines (SL); 38% gained ≥ 4 ±1.34 SLs, 35% ≥ 3 ±1.21 SLs, 22% ≥ 2 ±1.12 SLs, and 5% ≥ 1 ±0.75 SLs. The mean best spectacle–corrected visual acuity increased by + 4.3 ±1.3 SL. Sixty-eight percent gained ≥ 4 ±0.88 SLs and 30% ≥ 3 ±0.78 SL. No SLs were lost.

Conclusions: RT t-PRK plus ACXL significantly improved the quality of vision in patients with KC, preventing overcorrection and minimizing tissue consumption.

Key Words: ray tracing, t-PRK, RT PRK, crosslinking, CXL, keratoconus, M nomogram, pachymetry-guided crosslinking, ACXL, crosslinking plus, PRK/CXL

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Transepithelial photorefractive keratectomy (t-PRK) combined with individualized pachymetry-guided accelerated crosslinking (ACXL) represents an expanding refractive therapeutic opportunity in patients with keratoconus (KC) with poor or insufficient best spectacle–corrected visual acuity (BSCVA) who are intolerant to rigid gas-permeable contact lenses (RGP CL). The aim of this treatment is to improve uncorrected distance visual acuity (UCVA) and BSCVA by avoiding or postponing the need for keratoplasty.[1–4] The combined Ray-Tracing-Guided (RT t-PRK) plus ACXL consists of a minimally invasive ray-tracing–based customized transepithelial excimer laser central corneal remodeling (CCR) to improve the whole natural and spectacle-corrected quality of vision (QoV), reducing the high-order aberrations (HOAs) while consuming a small amount of corneal stroma.[5–7]

The use of combined topography-guided t-PRK plus crosslinking (CXL) represents a therapeutic reality performed in selected cases in many countries over the past decade.[8] The long-term follow-up studies have demonstrated the efficacy and safety of these procedures in improving the UCVA and BSCVA of patients with KC performed simultaneously (on a same-day basis) or sequentially (6 months at least after CXL).[9–18]

CXL has paved the way for these treatments by strengthening the corneal stroma and stabilizing the progression of KC.[19–21] The all-surface laser ablation in patients with KC is planned by using topography-guided algorithms, optimizing the optical zones and reducing the HOAs while minimizing the consumption of stromal tissue, and beyond improving patient's

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UDVA and BSCVA, another purpose of this therapeutic option consists in giving another chance of contact lens fitting on a more regular reshaped corneal surface.[22] The introduction of ray-tracing technology in treatment planning allows the calculation of the refractive contribution of the posterior corneal surface and epithelium, thus avoiding undesirable overcorrections often reported in the literature with topography-guided techniques and minimizing stromal tissue ablation.[23]

We present the results of a tissue-preservation algorithm based on ray-tracing–guided transepithelial excimer laser CCR plus pachymetry-guided individualized ACXL treatment (M nomogram, developed by Mazzotta C at Siena Crosslinking Center, Italy)[24] in a case series of patients with stable KC who were intolerant to RGP CL and had poor QoV. The procedure was performed purely on the basis of improving visual function in patients with stable KC in the past 12 months.

METHODS

Study Design

The prospective RT t-PRK plus ACXL interventional study was approved by the Institutional Review Board of the Siena Crosslinking Center, Siena, Italy, and included 38 eyes of 38 young adult patients with stage II KC according to Krumeich–Amsler staging,[25] with a mean age of 35 years (range 26–46 years) undergoing simultaneous or same-day ray-tracing–guided t-PRK[6] plus individualized pachymetry-based ACXL (M nomogram).[24] All treatments regarded the worst eye were performed at the Siena Crosslinking Center by a single operator (C.M.) using the iVis Suite iRES Excimer Laser (iVis Technologies S. r. l., Taranto, Italy). Diagnostic data were assessed using a Precisio 2 tomographer (iVis Technologies S. r. l.) and Sirius tomographer (C.S.O., Florence, Italy).

Inclusion Criteria

Stage II KC, age 26 years or older, poor or insufficient BSCVA ≤0.5 Snellen lines (SLs), intolerance to RGP CLs, negative anamnesis for herpes virus infectious keratitis, severe dry eye, KC-associated corneal dystrophies, corneal opacities, and pregnancy. Keratoconus stability in the last year follow-up examination was considered by a Kmax variation ≤ 1 diopter (D), minimum corneal thickness (MCT) reduction ≤ 10 μm, and UDVA and CDVA worsening of ≤ 0.1 decimal equivalent or ≤ 0.5 spherical equivalent. Half of the patients had a marked tendency to rub their eyes and were asked to stop this chronic habit of abnormal rubbing. No previous CXL treatment. The MCT required for enrollment in the treatment protocol was ≥420 μm (epithelium included); therefore, the residual thickness was never less than 350 μm (epithelium included). The patients provided a specific informed consent form for both t-PRK and individualized pachymetry-based ACXL.

Preoperative Assessment

Preoperative tomographic examination was performed using the Precisio 2 Scheimpflug tomographer (iVis Technologies S. r. l.), assessing the Corneal Morphological Index of Regularity (CMI) that measures corneal refractive aberrations above the second order, providing an indication of the regularity of the corneal surface, which translates to the patient's quality of vision (QoV). CMI expressed in μm was calculated as the difference between the anterior corneal surface and the best-fit toroid defined within a predetermined domain (D). To obtain high-resolution maps required for customized corneal surgery, the Precisio 2 system exploits an ultrathin blue laser slit, analyzing the scattered light of all corneal layers, to measure epithelial thickness independently from the lacrimal film because scattering is absent in liquids; a 6D eye-tracker, built in to compensate the eye movements during the acquisition; and a voice-driven examination autoacquisition to negate possible subjective errors induced by the operator.[7]

Mean Outcome Measures

Preoperative and postoperative main outcome measures included UCVA, BSCVA, maximum corneal curvature (K max), mean pupil power, topographic cylinder, coma and HOAs, MCT, and posterior elevation (PE) measured using the Sirius tomographer (C.S.O.). Anterior segment corneal optical coherence tomography (OCT) was also performed (OptoVue, Fremont, CA) to assess the demarcation line (DL). The mean follow-up period was 52 months (range 12–96 months).

Statistical Analysis

A 2-tailed paired sample Student t test was used to compare each baseline measurement to the respective follow-up measurements. Differences with $P < 0.05$ were considered statistically significant at $P < 0.05$. Data were collected and analyzed with PRISM 6.0, GraphPad Software (La Jolla, CA).

Surgical Planning

All treatments were planned using the Corneal Interactive Programmed Topographic Ablation Web-based application (CIPTA 2 Web; iVis Technologies S. r. l.). To generate a custom ablation plan, elevation data describing the anterior cornea and anterior stroma and the thickness data of the epithelium and stroma were imported into the software. The ablations were programmed to treat the corneal cylinder and HOAs, which are the components most affected by epithelial remodeling. Differently from the topography-guided ablation, the coma aberration, as a dominant HOA of KC, and the sum of the HOAs originating from the anterior and the posterior corneal surface, obtained by the ray-tracing–based refractive corneal mapping, are treated. Moreover, exploiting the Stiles–Crawford effect, the refractive zone is limited in the range between 1.0 mm and 4.0 mm to minimize the surgical invasiveness and, if required, also correct second order aberrations, in particular astigmatism. The customization of the radial length of the connecting zone, with a constant gradient of the power, minimizes the risk of regression, reduces the risk of glares and halos, and facilitates the

epithelial homogeneous regrowth. To enhance QoV and treatment stability, the software overcomes the separation between the "optical zone" and "transition zone," defining a unique continuous ideal shape, maximizing smoothness and minimizing ablation. The planned ideal shape is characterized by an inner area, the refractive zone defined by means of a ray-tracing algorithm to optimize the QoV, surrounded by a customized connecting zone, defined by applying a constant gradient curvature to maximize the stability of surgical treatment. Ray-tracing–guided central corneal remodeling aims to regularize the anterior cornea, taking care of the refractive contribution of the posterior corneal surface aberration to optimize the final QoV and minimize the consumption of stromal tissue. The posterior corneal shape introduces posterior corneal morphological irregularities or HOAs, which partially compensate for the anterior corneal morphological irregularities of the opposite sign. This issue is particularly relevant in the management of complex cases, such as corneas with KC, where the posterior surface may reach consistent comatic diverging power. In other words, the ideal shape generated by the ray-tracing software remodels the anterior cornea, leaving onto the anterior surface the exact amount of CMI needed to compensate for the posterior CMI to null the total CMI (tCMI). Moreover, the remaining anterior corneal morphological irregularities minimized the amount of tissue removed and optimized the final QoV. The ablation plan is derived by tracing the light beam of up to 120,000 rays (number depending on the size of the ablation area) entering the anterior cornea from the air, parallel to the optical system, traveling through the epithelium and stroma and exiting to the aqueous from the posterior corneal surface and finally focusing onto the best focusing point along the visual axis, using the refractive indices of air/epithelium, epithelium/stroma, and stroma/aqueous. The result is the total corneal refractive map acquired by the Precisio 2. By reverse ray-tracing, from the best focusing point, the ideal corneal shape, within the selected refractive zone, is determined to null (over the second order) and the planned second order aberrations. The ablation map is defined as the intersection between the preoperative shape and ideal corneal shape; hence, this ablation will leave untreated the anterior corneal irregularities that compensate for the posterior aberrations. As a secondary benefit, less tissue will be removed, compared with anterior corneal topography-guided ablation. Differently from the wavefront maps provided by the Hartmann–Shack aberrometer, which analyzes all detected points in 1 single shot, thus causing lack of correlation between the detected points and the Hartmann–Shack lenslet array, the CIPTA Web application provides a point-by-point independent ray-tracing analysis on a 50-μm square grid, increasing data accuracy and repeatability. The total corneal ray-tracing calculation is achieved using the corneal data acquired by an ultrathin blue laser slit technology analyzing corneal scattering that provide 120.000 independent datapoints × each examined surface, including the anterior cornea, stroma, posterior cornea, and iris. The whole data input required for the customized programmed trasepithelial excimer laser central corneal remodeling include: high-definition anterior, stromal, and posterior corneal shape; epithelial, stromal, and total pachymetry; and ray-tracing anterior, stromal, and posterior refractive maps acquired by Precisio 2.5–7 The ray-tracing treatment planning also considers the biometric data: axial length, anterior chamber depth, and lens thickness (LT) provided by modern laser interferometry or SS-OCT–based biometers. The ablation profile is based on reverse ray tracing, involving validated tomographic data of all corneal surfaces by the Precisio 2 tomographer, ie, dynamic pupillometric data and biometric data for phakic eyes including anterior chamber depth, LT, Gullstrand lens profiles, and axial length, whereas for pseudophakic eyes, the axial length, the anterior chamber depth, the IOL thickness, and profile are included. The manifest and cycloplegic refraction were also included, and the fellow eye biometry and refraction data were compared. Dynamic pupillometry was acquired using a pMetrics binocular pupillometer (iVis Technologies S. r. l.), which provides an ideal pupil diameter calculation based on different illumination settings, taking into account patients' lifestyle and work activities (eg, night drivers or day workers). According to the Stiles–Crawford effect,[26] the central 1.00 mm area being the most relevant portion of the cornea for distinct vision, a small refractive zone between 1.0 and 4.0 mm can be selected to further reduce the stromal tissue ablation, working on a customized connecting zone with a constant gradient of curvature within a total ablation of up to 10.0 mm in diameter, with the aim to minimize the risk of glare and halos as well as the risk of regression. A minimum postoperative residual stromal thickness of 300 μm is recommended in all cases of this protocol (350 μm measured with the epithelium).

Surgical Technique

Treatments were performed under topical anesthesia with 4% oxybuprocaine chlorhydrate 1.6 mg/0.4 mL drops. After applying a closed valve eyelid speculum and drying the corneal surface with a Merocel sponge, full customized CCR was achieved using a single-step no-touch t-PRK by the iRES Excimer Laser (iVis Technologies S. r. l.), which has a small spot size (0.65 mm) and a frequency of up to 1000 Hz, delivered to the cornea. The laser uses a patented algorithm that delivers a constant fluence per unit of time to prevent overheating and maximize the smoothness of the ablation profile. Immediately after laser ablation, pachymetry-guided accelerated crosslinking was performed to strengthen the corneal stroma. After 10 minutes of corneal soaking with the Safecross 0.25% isotonic Riboflavin solution (iVis Technologies S. r. l.), the epithelium-off ACXL treatments were performed according to the residual stromal thickness after laser ablation and individualized using the pachymetry-based M nomogram guidelines for all-thickness ectatic corneas,[24] maintaining a constant fluence of 5.4 J/cm^2, a UV-A power range between 9 and 30 mW/cm^2, and an exposure time between 6 and 12 minutes with continuous or pulsed UV light exposure. One drop of riboflavin solution was administered every 3 minutes during the UV-A irradiation. At the end of irradiation, the corneal surface was washed with balanced saline solution, medicated with preservative-free netilmicin plus dexamethasone and cyclopentolate eye drops, and

dressed with a therapeutic bandage soft contact lens for 5 days. After bandage contact lens removal, the postoperative treatment continued with tapering of 2% fluorometholone eye drops for 12 weeks and artificial tear drops q.i.d.

RESULTS

At 4-year follow-up, the mean UDVA and BSCVA increases were + 3.5 ±1.28 SLs and + 4.3 ±1.3 SLs, respectively, as shown in Figure 1. Differences were considered statistically significant at $P \leq 0.05$.

The UDVA gain was ≥ 4 ±1.34 SLs in 38% of eyes, ≥ 3 ±1.21 SLs in the 35% of eyes, ≥ 2 ±1.12 SLs in the 22% of eyes, and ≥ 1 ±0.75 SLs in the remaining 5%, as shown in Figure 2. Differences were considered statistically significant at $P \leq 0.05$.

The BSCVA gain was ≥ 4 ±0.88 SLs in 68% of eyes, ≥ 3 ±0.78 SLs in 30%, ≥ 2 ± ≥0.33 SLs in 10% of eyes, and ≥ 1 ±0.24 SLs in 2% of eyes. No lines are lost, as shown in Figure 2. Differences were considered statistically significant at $P \leq 0.05$.

The mean preoperative Kmax value was 49.07 ±0.9 D; at 4-year follow-up, the mean Kmax value was 46.43 ±0.7 D, as shown in Figure 3. Differences were considered statistically significant at $P \leq 0.05$.

The mean preoperative coma value was 0.67 ±0.09 μm; at 4-year follow-up, the mean coma value was 0.35 ±0.02 μm, as shown in Figure 4. Differences were considered statistically significant at $P \leq 0.05$.

The mean preoperative tomographic cylinder value was −3.27 ± 1.55 diopters (D); at 4-year follow-up, the mean tomographic cylinder value was −2.14 ± 1.30 D, as showed in Figure 5. The differences were not statistically significant.

The mean preoperative MCT was 467.60 μm (range, 421–509 μm), and the mean postoperative MCT was 401 μm (range, 351–440 μm), as shown in Figure 6. Differences were considered statistically significant at $P \leq 0.05$.

The mean preoperative posterior elevation was 56.80 ±1.3 μm. The postoperative posterior elevation was 58.80 ±1.2 μm, as shown in Figure 7. The difference was not statistically significant ($P > 0.05$), showing stability during the entire follow-up period.

The preoperative mean pupil power was 47.27 ± 0.5 D; the postoperative mean pupil power was 44.20 ± 0.6 D, as shown in Figure 8. Differences were considered statistically significant at $P \leq 0.05$.

The differential map in the top half of Figure 9 shows the ray-tracing–guided ablation, whereas the differential map in the bottom half of the same figure shows the preoperative to postoperative differences in point spread function and the relative simulated QoV. The posterior elevation follow-up maps show postoperative stability of the ectasia over time despite tissue ablation, as shown in Figure 10.

Endothelial cell density showed no statistically significant reduction from the mean baseline cell count of 2622 ± 31 cells/mm^2 to 2597 ± 39 cells/mm^2. A DL was documented during the first month of postoperative evaluation using anterior segment OCT. The mean DL was 238.2 ±33 μm.

No intraoperative and postoperative adverse events were recorded during the follow-up. The demographic data and overall study results are summarized in Tables 1 and 2, respectively.

DISCUSSION

The use of combined topography-guided t-PRK plus CXL represents a therapeutic reality performed in selected cases in many countries for over a decade.[1,3,8] Kanellopoulos et al and Kymionis et al[4] were the pioneers of these treatments, publishing the first international experiences[1,2] resulting in their respective protocols: the "Athens protocol"[10] and the "Cretan protocol". Long-term follow-up studies[8,9,12] demonstrated the efficacy and safety of the topography-guided t-PRK and t-PTK procedures in improving UCVA and BSCVA in patients with KC and reducing HOAs, without adverse events and no cases of long-term ectasia instability despite stromal tissue ablation. Only a small percentage of overcorrections have been reported.[8,14] Finally, the possibility of precisely

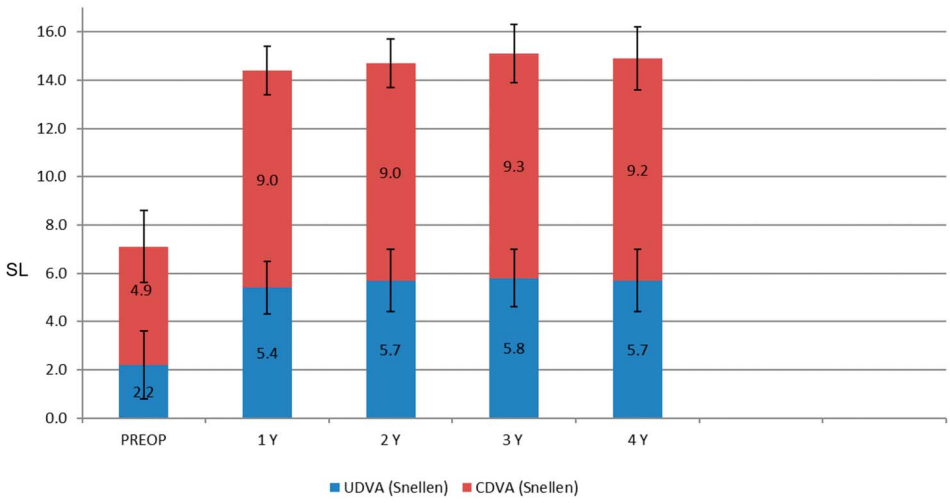

FIGURE 1. Bar graph demonstrating the course of uncorrected distance visual acuity (Blue bars) and best spectacle–corrected distance visual acuity (red bars) after ray-tracing transepithelial excimer laser central corneal remodeling plus pachymetry-guided accelerated corneal crosslinking for keratoconus.

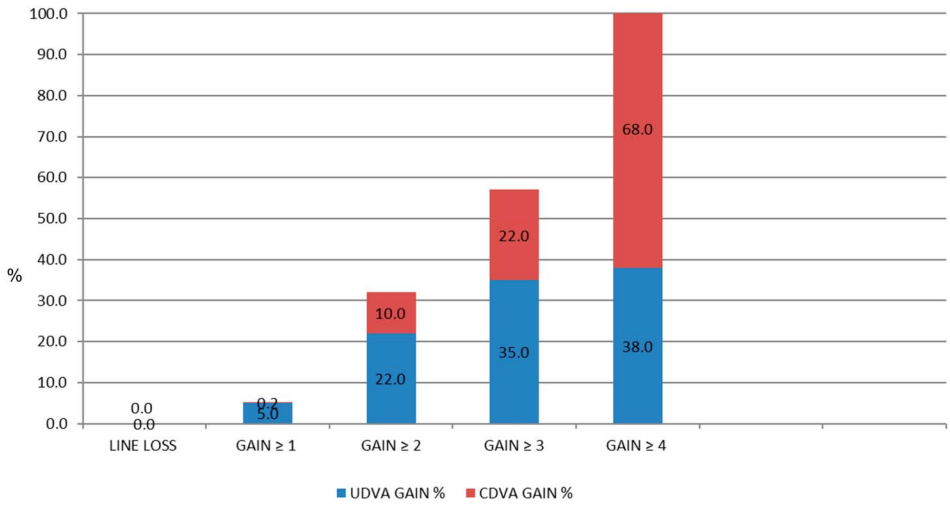

FIGURE 2. Bar graph showing preoperative to postoperative changes in Snellen lines of uncorrected distance visual acuity (Blue bars) and best spectacle–corrected distance visual acuity (red bars).

calculating the refractive contribution of the posterior corneal surface and corneal epithelium in topography-guided treatments by means of ray-tracing–guided customized ablations could make the difference by avoiding overcorrections, improving functional results, and sparing stromal tissue, as shown by pivotal studies[5,6,23] and confirmed in our case series in the long-term follow-up.

Indeed, the mean UDVA and BSCVA increases were +3.5 and +4.3 SLs, respectively, superior to the average results reported in the long-term studies without using a ray-tracing software for t-PRK. Ray-tracing–guided transepithelial excimer laser corneal ablation combined with pachymetry-guided accelerated corneal crosslinking (RT t-PRK plus plus Mazzotta pachymetry-based ACXL nomogram) showed that 68% of treated patients with BSCVA had at least 4 SLs or more. No lines were lost, and no overcorrections were reported during the follow-up. The stability of ectasia was confirmed using posterior elevation and pachymetry differential maps.

As first reported by Kanellopoulos,[10] our study also reported the long-term stability of ectasia after ray-tracing t-PRK ablation by maintaining a minimum corneal thickness of 350 μm epithelium. According to Kymionis et al, the functional results of the combined t-PTK and CXL were effective and safe in patients with KC over a long-term follow-up and were indicated in patients with RGP lens intolerance and poor spectacle-corrected distance visual acuity, thus avoiding or at least postponing the need for corneal transplantation.[4,12]

In accordance with the larger comparative study[11] including a total of 325 eyes with KC, comparing a group of 127 eyes that underwent CXL with subsequent topography-guided PRK performed 6 months later (sequential group) and a second group of 198 eyes that underwent CXL and PRK in a combined procedure on the same day (simultaneous group) showed that same-day simultaneous topography-guided PRK and CXL was superior to sequential CXL with later PRK in the visual rehabilitation; therefore, our patients were treated simultaneously on a same-day basis. In addition, the results of the "Cretan protocol",[4,9,12] as confirmed by other retrospective cohort studies, proved that simultaneous topography-guided partial PRK or PTK and

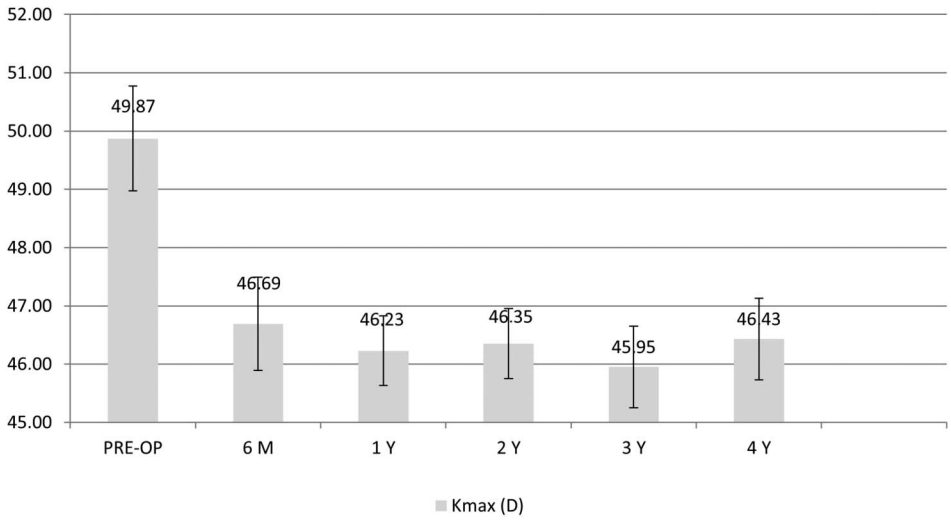

FIGURE 3. Bar graph showing preoperative to postoperative changes of K max diopters (D).

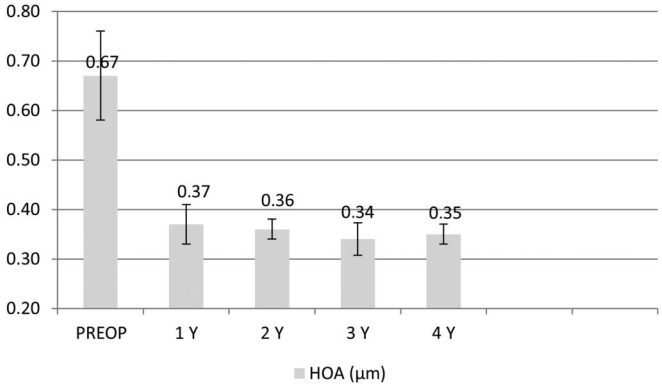

FIGURE 4. Bar graph showing preoperative to postoperative changes of high-order aberrations in μm.

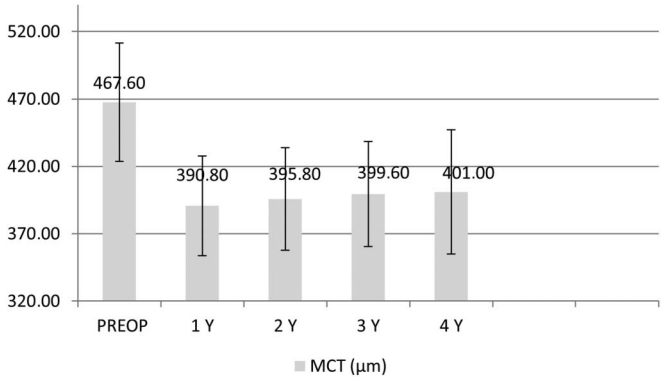

FIGURE 6. Bar graph showing preoperative to postoperative changes of minimum corneal thickness in μm.

CXL was effective, safe, and stable in patients with keratoconus, significantly reducing the higher-order aberrations and astigmatic error, thus improving UDVA and BSCVA.[13–18]

Other studies have demonstrated that excimer laser CCR can also be performed at least 6 to 12 months after CXL treatment.[15] Retrospective, noncomparative consecutive case series in patients who underwent corneal wavefront-guided trans-PRK for the correction of aberrations at least 4 to 6 months after CXL reported that corneal wavefront-guided transepithelial PRK ablation profiles after conventional CXL also yield good visual, optical, and refractive results.[16,17]

Although these combined treatments have been performed and are widespread for over a decade, the literature shows inhomogeneous protocols[5,6,10–18,22] and different settings both in excimer laser planning and crosslinking application, which can be considered a limitation. However, this diversity of protocols is understandable because of the diversity of individual clinical cases, which inevitably require a personalized approach according to KC baseline parameters, patient age, high-order aberrations, posterior corneal surface aberrations, baseline minimum corneal thickness, apex cone localization, and RGP CL intolerance. One of the major problems is related to the irregularity of the corneas affected by KC and the need for software that allows the calculation of the variable refractive contribution of the posterior surface of the cornea to improve the refractive result. The main goal is to consume as little tissue as possible and avoid unpleasant overcorrections. The ray-traced–customized corneal t-PRK has been shown to be able to solve many of the problems reported and to place itself as a possible reference standard for the personalized programming of these special treatments.[6,7,23]

In our study, topography-guided custom surface ablation followed by individualized constant-fluence pachymetry-guided ACXL uses a no-touch all-surface ablation with a transepithelial approach to minimize stromal consumption, taking into account the masking effect of the corneal epithelium in KC irregular corneas. The RT t-PRK plus M nomogram ACXL protocol was based on topography-guided custom ablation with ray-traced planning. Minimal selective ablation of the cornea is performed to transform the preoperative irregular corneal morphology into a regular aconic shape of the desired curvature, which is defined as the expected postoperative anterior corneal curvature according to the programmed treatment. Differently from another protocol,[22] to achieve a minimal tissue removal, the CCR is performed setting a narrow optical zone (1.0–1.5 mm in diameter), whereas the quality of the postoperative corneal

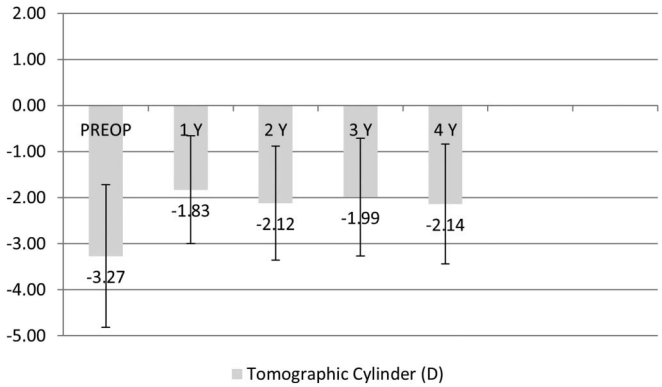

FIGURE 5. Bar graph showing preoperative to postoperative changes of tomographic cylinder diopters (D).

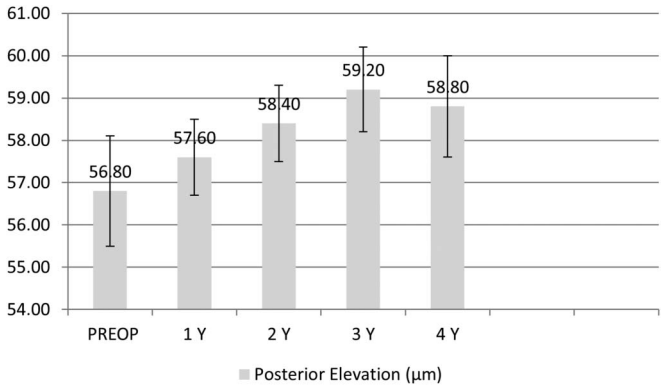

FIGURE 7. Bar graph showing preoperative to postoperative changes of corneal posterior elevation in μm.

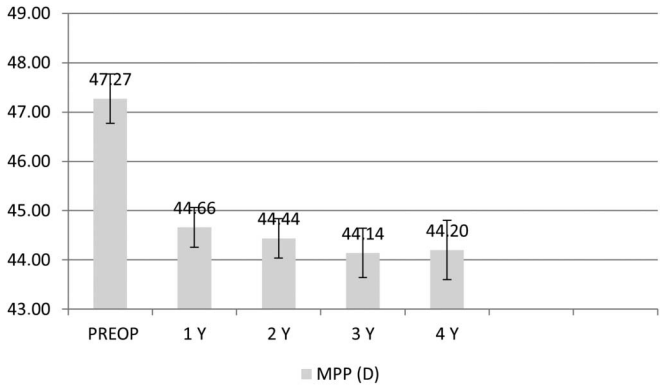

FIGURE 8. Bar graph showing preoperative to postoperative changes of mean pupil power diopters (D).

optics is addressed by a gradually fading custom ablation effect toward the periphery, within a total ablation zone of up to 9.8 mm in diameter.[5–7] The large "connecting refractive zone" between the central optical zone and the untreated periphery features offers a smooth customized transition with a constant slope in each radial direction, resulting in a linear decrease of curvature. Programmed customized ablation is achieved by software based on ray-tracing calculation of the total corneal power, balancing the refractive contribution of the posterior and anterior corneal surfaces. Ray tracing is based on the Snell law of refraction and allows the evaluation of the pathway of light rays after their passage through the eye from the anterior corneal surface to the retina. By doing this, it is possible to know the exact refractive contribution of each surface (cornea and lens) and customize excimer laser ablation to reduce or normalize the distortion due to ectasia. This is achieved by not performing a full regularization of the anterior corneal morphological irregularities, which would induce an overcorrection by making the comatic component of the posterior corneal surface prevail and would increase tissue consumption; instead, a planned small amount of aberration on the anterior corneal surface is left to compensate for the posterior surface aberrations. In fact, the posterior corneal shape introduces posterior corneal morphological irregularities, which partially compensate for aCMIs or HOAs

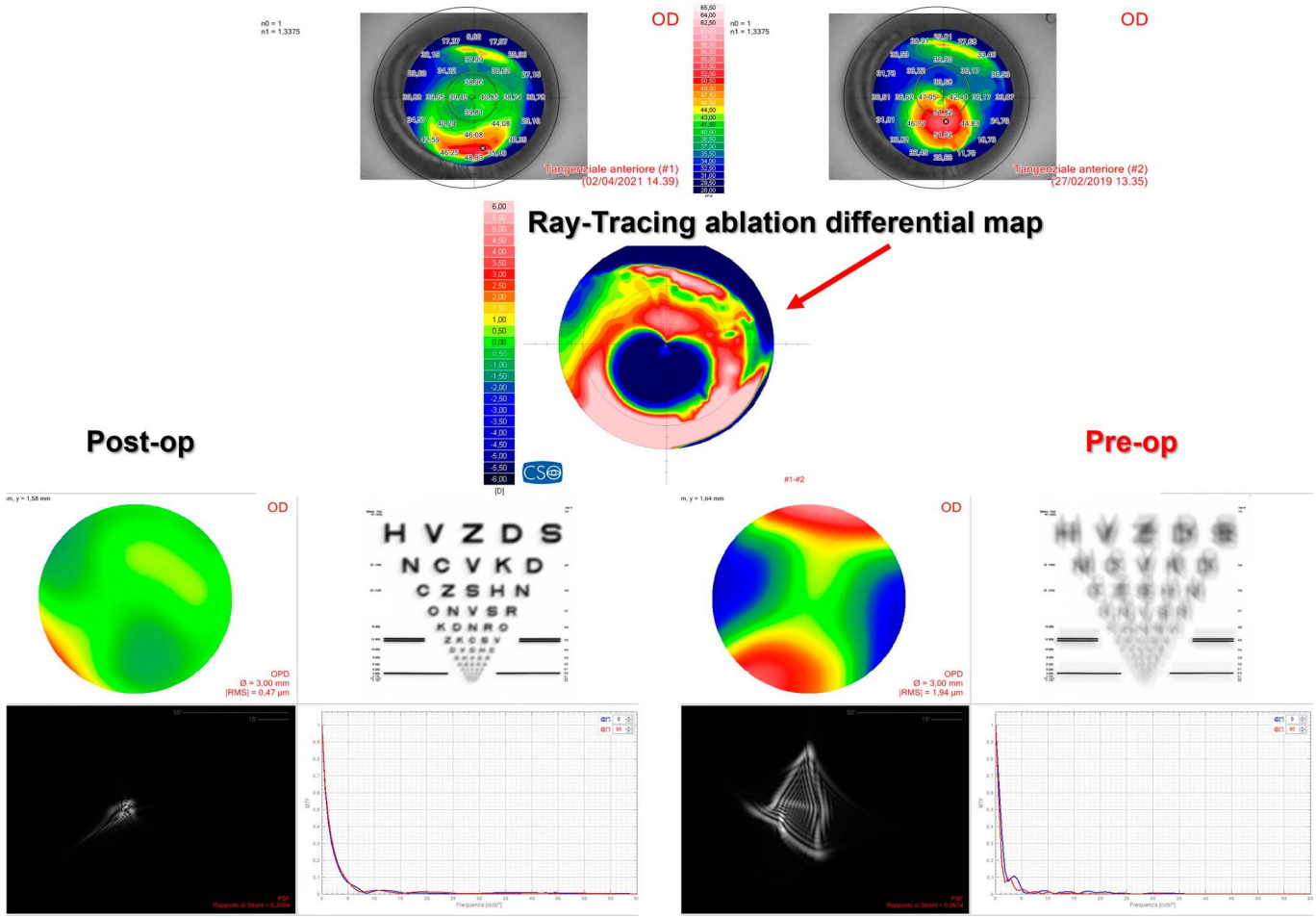

FIGURE 9. Differential map in the top half of the figure shows the ray-tracing–guided ablation. The differential map in the bottom half of the figure shows the preoperative to postoperative differences in point spread function and quality of vision.

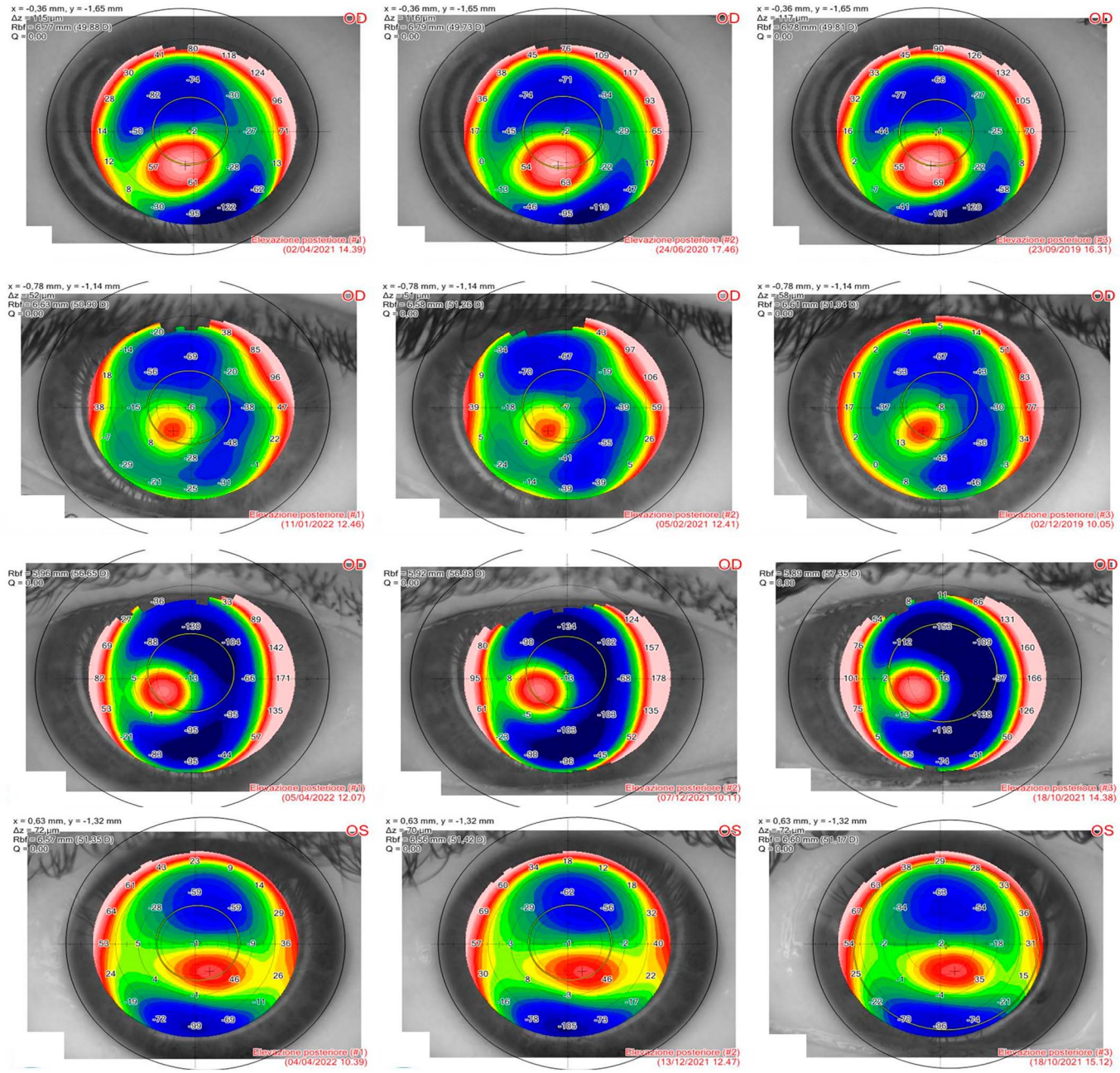

FIGURE 10. Posterior elevation follow-up maps show postoperative stability of the ectasia over time despite tissue ablation.

of opposite sign. This issue is particularly relevant in the management of complex cases, especially in ectatic corneas where the posterior surface may reach consistent comatic diverging power. Thus, the ideal shape generated by the ray-tracing software remodels the anterior cornea, leaving onto the anterior surface the exact amount of CMI needed to compensate the posterior CMI to effectively null the total CMI (tCMI). The remaining anterior corneal morphological irregularity minimizes the amount of tissue removed and optimizes the patient's overall QoV. The CIPTA Web ray-tracing algorithm traces the light beams refracted through the anterior and posterior corneal surfaces on a 50-μm size grid within the refractive zone to determine the best focusing point. Therefore, we can modify the anterior corneal profile by considering the actual posterior corneal surface. This helps in preventing undesired overcorrections, as reported in previous long-term studies, without using the ray-tracing algorithm. Moreover, the ray-tracing technology currently makes it possible to consider the refractive role of the epithelium, which represents a diverging comatic lens that may reach a high grade of compensation in irregular corneas with KC, thus further optimizing the clinical results.

TABLE 1. Baseline Demographic Data

Baseline Total Characteristics 40 Eyes of 40 Pat.	Value (mean)	SD or %
Mean age (yr)	32.50	±10.6
Male	30	75%
UDVA Snellen lines	2.2	±1.4
CDVA Snellen lines	4.9	±1.5
Kmax (D)	49.87	±0.94
MCT (μm)	467.60	±44.00
Coma (μm)	0.67	±0.09
MPP (D)	47.27	±0.50
Tomographic Cyl (D)	−3.27	±1.55
Endothelial cell count (cell/mm^2)	2622	±235

TABLE 2. Study Results

	Preoperative	Postoperative (4 yr)
UCVA (Snellen)	2.2	5.7*
CDVA (Snellen)	4.9	9.2*
Kmax (D)	49.87	46.43*
Coma (μm)	0.67	0.35*
Tomographic Cyl (D)	−3.27	−2.14
MCT (μm)	467.60	401.00*
MPP (D)	47.27	44.20*
PE (μm)	56.80	58.80

*Statistically significant $P \leq 0.05$.

All treatments in our series were planned to leave at least 300 μm of minimum residual stroma (350 μm epithelium included), followed by an individualized ACXL protocol based on the pachymetry-guided M nomogram.[24] The techniques that remove the epithelium manually or by alcohol, without considering that the epithelium in KC corneas acts as a masking agent following a stromal gradient of curvature thus compensating the stromal morphological irregularities, induce higher tissue volume ablation and a higher risk of overcorrections, with a potential hyperopic shift, without considering the contribution of the posterior corneal surface aberration that differs case by case in the heterogeneous KC phenotypes. Indeed, the transepithelial selective excimer laser photoablation procedures (t-PRK and t-PTK) showed superior results, ensuring a small amount of tissue consumption and better functional outcomes in customized central corneal remodeling.[22] Moreover, software based on calculation of mean pupillary power or ray-tracing technology, which can effectively nullify anterior and posterior corneal surface aberrations, is mandatory to avoid bad surprises, as proved by our study results. The ray-tracing technology used for the study was introduced by a small Italian company (iVis Technology S.r.l.) based on total (anterior and posterior) corneal ray tracing, where an appropriate amount of anterior corneal optical irregularities is left untreated to compensate for the posterior counterparts.[5–7] In this way, regular total corneal optics are achieved. The system also registers and treats the epithelium and stroma separately.[7]

Regarding CXL,[19] the same protocol was not used for all patients. The pachymetry-guided protocol[24] enables us to customize the ACXL strategy in many ways by setting the depth of the DL according to residual postablation stromal pachymetry, thus sparing the endothelium, using accelerated protocols to shorten UV-A illumination time and the pulsed light mode of exposure. Therefore, it is possible to reduce the risk of haze that was higher with the conventional Dresden 3 mW/cm^2 protocol[19–21] of 1 hour; indeed, the original 3 mW/cm^2 Dresden protocol is still not recommended for these combined procedures because of the higher possibility of haze development.[22] Another important recommendation, as recently demonstrated, is that the use of mitomycin C after CXL, and particularly in combined simultaneous topography-guided t-PRK with ACXL, should be avoided because it increases corneal haze formation.[27]

The "M nomogram" proposed by Mazzotta[24] (as awarded at European Society of Cataract and Refractive Surgery in Paris 2019 with the "J. Colin Award for keratoconus") is a pachymetry-based accelerated individualized CXL approach in which the depth of the DL is customized according to the baseline minimum corneal thickness maintaining the constant fluence standardized in the Dresden protocol (5.4 J/cm^2) and simply adapting the UV-A power range from 9 to 30/mW/cm^2 and the exposure time interval from 10 to 6 minutes by using continuous and pulsed light irradiation according to documented clinical and morphological literature data and accelerated protocols (9 mW/5.4J/cm^2, 15 mW/5.4J/cm^2, 18 mW/5.4J/cm^2, and 30 mW/cm^2).[28–34] The riboflavin soaking is maintained at 10 minutes after all-surface laser ablation using a dextran-free isotonic 0.25% solution with HPMC. Confocal microscopy and OCT proved that in eyes treated with 9 mW/cm^2 continuous light–accelerated CXL,[28] the DL will be at 300 ± 30 μm and eyes treated with 30 mW/cm^2 pulsed light–accelerated CXL will have demarcation depths of 200 ± 30 μm.[29,31,32] Eyes treated with 15 mW/cm^2 pulsed light–accelerated CXL[33] had depths at 250 ± 30 μm and with 18 mW/cm^2 had depths at 220 ± 30 μm.[30]

The "M nomogram" protocol allows maintaining a constant fluence of 5.4J/cm^2, established as a reference standard in the Dresden protocol in KC corneas from a minimum stromal thickness of 200 μm, always conferring the same dose and strength to the stroma, without decreasing the fluence.[24] In this way, the ACXL can be individualized in a range between 200 and 400 μm, particularly useful in the combined treatments and in the standardized treatment of thin ectatic corneas.

The main distinguishing features of our protocol compared with the pivotal Athens protocol are essentially the use of a total corneal ray-tracing–guided ablation, which guarantees sparing of stromal tissue by not completely removing the anterior corneal aberrations, taking care of the posterior surface refractive contribution, and the combination of individualized pachymetry-based accelerated crosslinking M nomogram allowing a safe and faster reinforcement of all-thickness ectatic corneas between 200 and 400 μm. The standard CXL Dresden protocol, owing to the impossibility to include thin corneas under 400 μm of MCT, frequent

unpredictable and undesirable long-lasting corneal flattening with relative aberrometric changes, and greater risk of haze that could negatively affect the clinical results, is is no longer recommended or indicated in these combined CXL plus excimer laser treatments.

In conclusion, this study proves that ray-tracing–guided transepithelial excimer laser CCR plus pachymetry-guided M nomogram ACXL treatment improves the overall QoV in patients with low-to-moderate KC intolerance to RGP CLs without sacrificing biomechanical stability of the cornea in long-term follow-up and can be considered another useful tool in modern KC management.

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