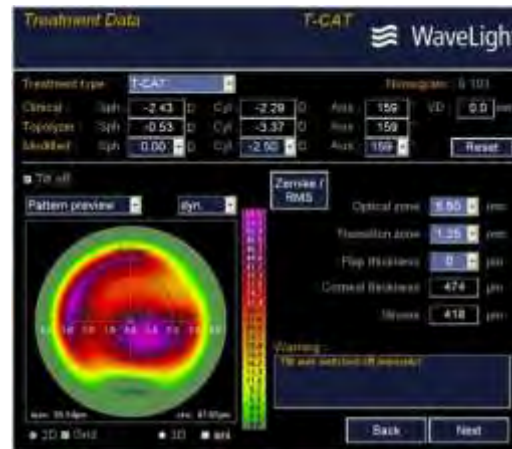
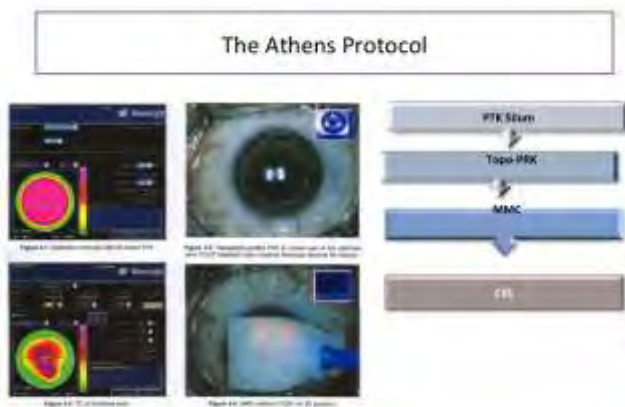


Short and long term complications of combined topography guided PRK and CXL (the Athens Protocol) in 412 keratoconus eyes (2-7 years follow-up)

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Anastasios John Kanellopoulos, MD

Director, Laservision.gr Institute, Athens, Greece

Clinical Professor NYU Medical School, NY

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Introduction:

- Corneal collagen crosslinking (CXL) has become a new addition to the armamentarium for the treatment of keratectasias, in particular keratoconus and post—LASIK ectasia. CXL with the use of riboflavin (vitamin B2) and ultraviolet A (UVA) irradiation cross links the collagen fibers in the corneal stroma thereby strengthening and biomechanically stabilizing the cornea (1). This is especially useful in keratoconus (KC) where progressive corneal thinning and steepening leads to myopia and irregular astigmatism (2). Promoting a new approach for the treatment of KC, CXL has become a viable option in addition to the established treatments available including spectacle correction, rigid gas permeable contact lenses, intrastromal corneal ring segments (3) and penetrating keratoplasty (4).
- The goal of introducing topography-guided photorefractive keratectomy as a component to the CXL procedure is to normalize the corneal surface and to decrease the irregular astigmatism (5). The synergistic effect of combined topography-guided photorefractive keratectomy and collagen crosslinking (tgPRK-CXL), the Athens Protocol, may provide further improvement in visual acuity than with CXL alone (6).
- The purpose of this study is to demonstrate the common early and late complications associated with tgPRK-CXL in keratoconus patients. The primary outcome measures in this prospective cohort study are the presenting complications and the resulting corrected-distance visual acuity post tgPRK-CXL.



Surgical Procedure

- Topographic data from the proprietary WaveLight customized platform (Topolyzer) served as the basis for the topography-guided PRK. The resulting topographic data were drawn from an average of eight topographies with the following parameters: zero postoperative asphericity, no tilt correction, and a 5.5 mm optical zone. The goal was to treat 70% of cylinder and the remaining amount of sphere up to a maximum of 70%, so as not to exceed 50 μm in stromal removal.
- The surgical procedure was performed in a single institution by the same surgeon (A.J.K) under sterile conditions. Following placement of an aspirating lid speculum (Rumex, St Petersburg, FL), 20% alcohol solution was placed within a 9-mm titanium LASEK trephine (Rumex) for 20 seconds after which the epithelium was removed with a dry Weck-cell sponge. The laser treatment was then applied. Mitomycin C 0.02% solution in a soaked cellulose sponge was placed on the ablated tissue for 20 seconds followed by irrigation with 10 mL of chilled balanced salt solution.
- Next riboflavin sodium phosphate ophthalmic 0.1% solution (Priavision, Merlo Park, CA) was applied topically every 2 minutes for 10 minutes. Four diodes emitting UVA light of approximately 370 nm wavelength (365 to 375 nm) and 3 mW/cm² radiance at 2.5 cm was projected onto the corneal surface for 30 minutes. During this time, riboflavin solution was applied topically every 2 minutes with the aid of a Keracure timing device (Priavision).
- Following the completion of this procedure, a bandage contact lens was placed. The postoperative regimen consisted of topical ofloxacin (Allergan Inc, Irvine, CA) four times a day for 10 days, prednisolone acetate 1% (Pred Forte, Allergan) four times a day for 60 days, and oral Vitamin C 1000mg daily for 60 days. Sunglasses were highly recommended to protect from all natural light. The bandage contact lens was removed at approximately day 5 following complete reepithelialization.
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The Athens Protocol: same day

PTK > topoPRK > MMC > CXL (10mW/cm² x 10 min)

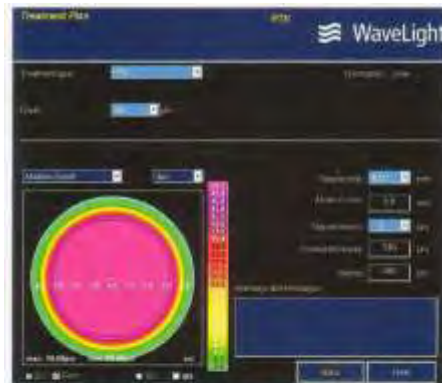


Figure 4.1: Epithelium removed with 50 micron PTK



Figure 4.3: Topography-guided PRK to correct part of the refractive error (TCAT treatment plan) maximal thickness removal 50 microns



Figure 4.2: TC at treatment plan

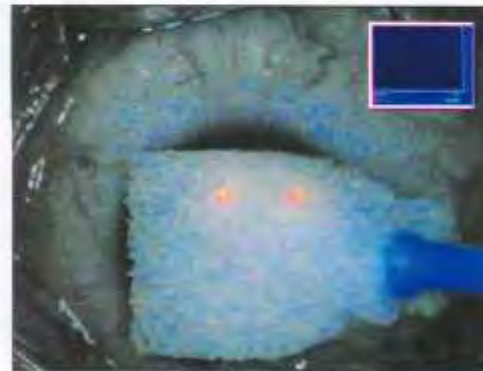


Figure 4.4: MMC solution 0.02% for 20 seconds

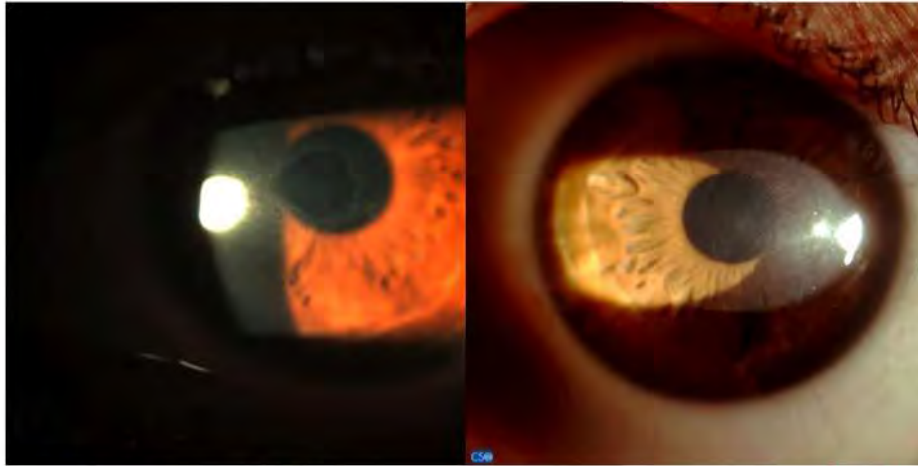
Please visit this link for a video presentation: <http://youtu.be/stmfRf4Aepg>



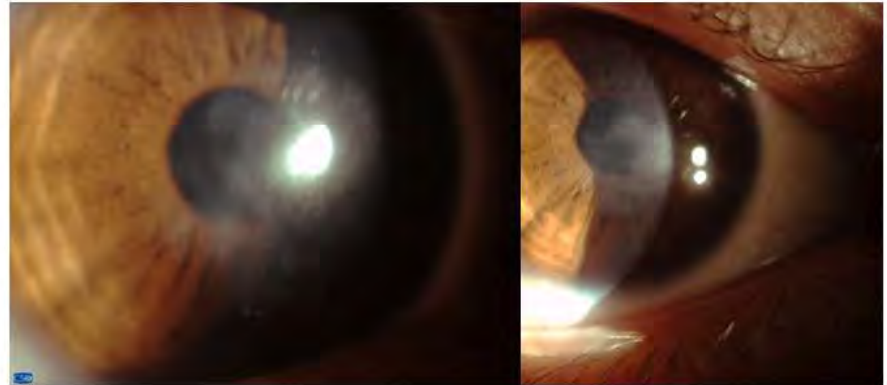
Results

- CDVA from 20/100 to 20/50. Early complications: 65% pain (Day 1)
- Ectasia Regression: 1.2% ectatic progression requiring retreatment. None required a corneal graft.
- The complications encountered were **delayed epithelial healing, postoperative pain, epithelial scarring, transient stromal haze**, and **progression of ectasia**. Epithelial healing occurred in 75% of cases by day 4, 15% by day 5, and 10% by day 10. No significant pain on postoperative day 1 was reported in 45% of the cases, moderate pain in 25%, and severe pain in 30%. Salzmann-like epithelial scarring, seen in 25% of the cases, persisted for an average of one month. The epithelial scar resolved with lubrication (30%), lubrication and bandage contact lens (BCL) (25%), autologous serum administration in addition to lubrication and BCL (25%), or surgical removal (20%).
- At 6 months post-procedure, 12 of the 412 cases had persistent subepithelial corneal scarring, but none that necessitated penetrating keratoplasty. Transient stromal haze was noted in 15% of the cases, which resolved by month 6 in 95% of these cases (8 of 412 cases showed stromal haze past month 6). Seven of 412 cases showed signs of ectatic progression, for which 2 required penetrating keratoplasty, 4 required repeat CXL, and 1 elected no treatment. One case with ectatic progression had undergone pregnancy out of 7 total pregnancies of the 412 cases.

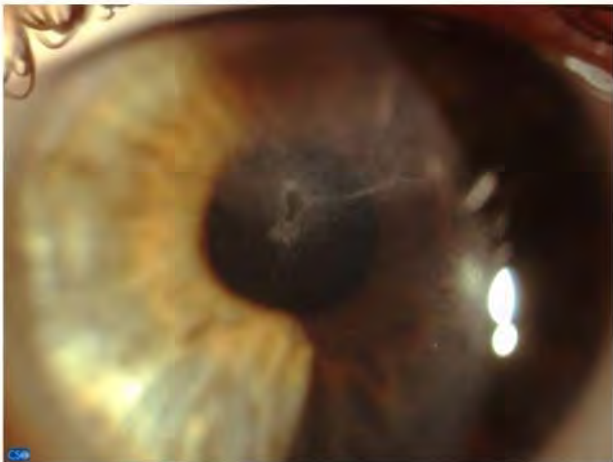
Healing delay-day4-ok on 1 month



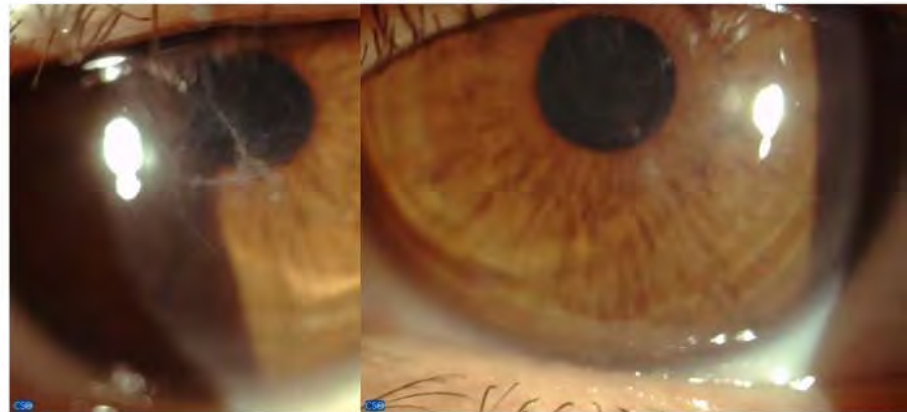
PRK-like haze 1 year after, in heavy sunbathing improved with steroids



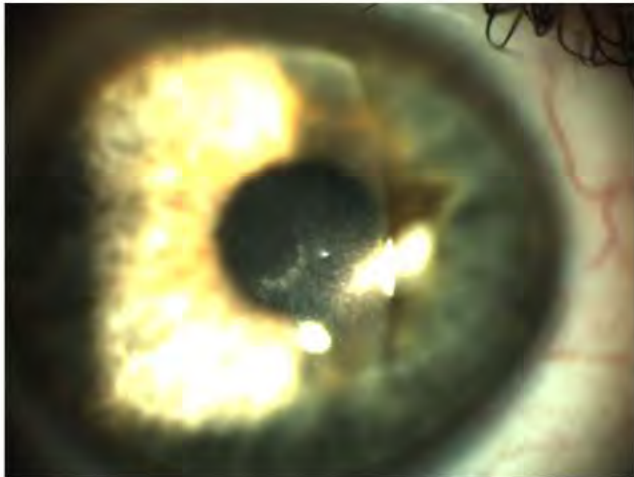
Week 2



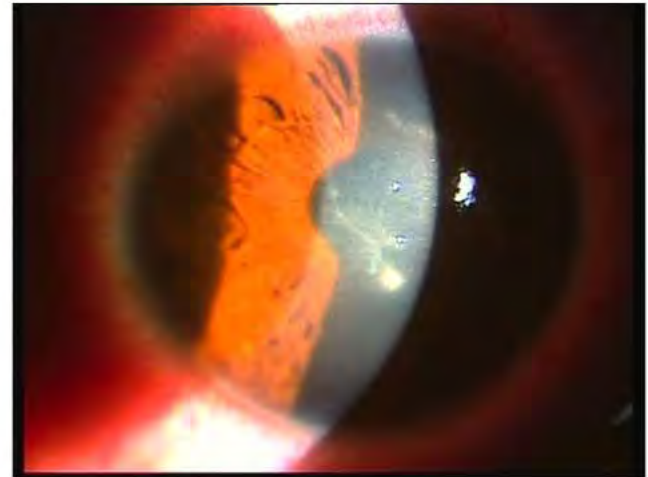
Week 2



Salzman's-like nodule(s) can persist to 3 months postop



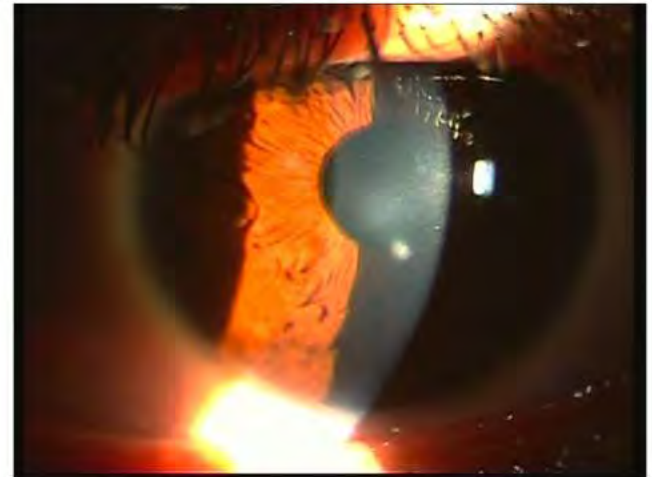
Delayed epithelial healing with
white spots



Haze



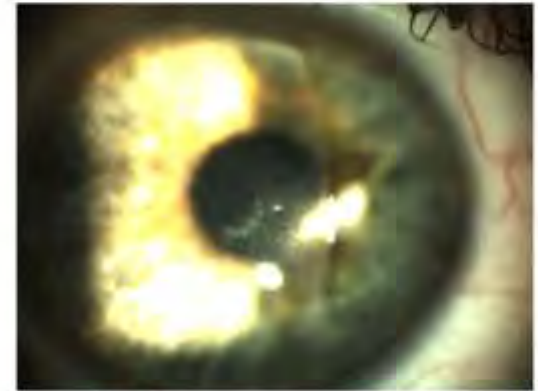
Faint Scar and white spot



- Like any surgical procedure, combined topography-guided photorefractive keratectomy and corneal collagen crosslinking (the Athens Protocol) has its own set of complications. The main early complications noted were postoperative pain, delayed epithelial healing, and Salzmann-like epithelial scarring.
- A significant percentage of patients experienced moderate to severe pain on postoperative day one after the Athens Protocol. This is most likely due to removal of the epithelium, much like the individual procedures PRK and CXL (7). A PTK (50 micron, 6.5mm diameter) was used to aid in the epithelium removal. However, recent studies have shown that there is no increase in postoperative pain with the use of alcohol in PRK (8). Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have been successful with pain management in traditional surface ablation procedures. Due to the nature of the keratoconic corneas and increased risk of delayed epithelial healing and perforation, topical NSAIDs were avoided (9).
- Delayed epithelial healing was reported if the epithelium did not heal completely after 5 days post procedure. After CXL alone, the mean epithelial healing time was found to be 3.25 days, ranging from 1 to 8 days (10). Our study found 10% of cases that did not heal completely by day 10. The PRK component may be contributing to the delay. These patients were observed closely to monitor for signs of additional corneal thinning or infection.

Salzman's-like nodule(s) can persist to 3 months postop

- Salzmann-like epithelial scarring, which persisted for an average of one month, was found in a significant percentage of cases.



The epithelial scar resolved with lubrication (30%), lubrication and bandage contact lens (BCL) (25%), autologous serum administration in addition to lubrication and BCL (25%), or surgical removal (20%). 2.9% of cases had persistent subepithelial corneal scarring beyond six months that did not respond to the various interventions. However, none of these cases necessitated penetrating keratoplasty. It is well known that CXL is cytotoxic to keratocytes (11), and confocal microscopy may be helpful in determining the composition of this epithelial scarring for further prevention.



- Notable late complications were stromal haze, and ectatic progression. Only a small percentage of cases (3.8%) demonstrated stromal haze past month six in this study. Permanent corneal haze after CXL alone has been reported (12). Other studies have reported posterior linear stromal haze formation after combined photorefractive keratectomy and collagen crosslinking (13). However, these studies did not include mitomycin C in their surgical protocol. Mitomycin C was used in this study since it has been shown to modulate corneal wound healing and to reduce corneal haze formation post PRK (14).
- The Athens Protocol was unable to halt the progression of keratoconus in a few cases (1.2%). Repeat CXL was required to treat this ectatic progression. Another study of simultaneous topography-guided PRK and CXL revealed no topographic or clinical signs of keratoconus progression post procedure (15). There are small differences between the two surgical procedures, and further studies are required to determine the causative factors for ectatic progression.
- The strengths of this study are the large cohort of patients and the long-term follow-up for a relatively novel procedure. This enabled us to present the late complications associated with this procedure. The main limitation is the observational study design, which does not include a control group. Generalizability is also limited since the study took place at a single clinical site. The effect of the Athens Protocol in advanced keratoconus with corneal thickness less than 350 μm is unknown at this time.

Conclusion

- **The Athens Protocol, combined topography-guided photorefractive keratectomy (with the Alcon/Wavelight platform) and corneal collagen crosslinking, is a promising technique to halt the progression of keratoconus and to provide improved, functional vision. The early complications associated with this procedure are postoperative pain, delayed epithelial healing, and Salzmann-like epithelial scarring, while the late complications are subepithelial corneal scarring, stromal haze, and ectatic progression. Techniques to manage the various complications are discussed with further studies necessary to control, manage, and prevent additional complications.**

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