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REVIEW ARTICLE

Collagen Cross-linking for Pellucid Marginal Degeneration

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ABSTRACT

Pellucid marginal degeneration (PMD) is a rare progressive condition resulting in inferior corneal thinning and astigmatism. Alongside keratoconus and keratoglobus, it is considered one of noninflammatory corneal ectasias. The focus of corneal thinning is greatest inferiorly resulting in diminished visual acuity and overall reduction in visual quality. Traditional methods of treatment or disease management have been similar to those proposed for keratoconus, contact lenses, escalating to intrastromal rings, lamellar keratoplasty or penetrating keratoplasty.

Collagen cross-linking (CXL) has steadily gained acceptance as the treatment of choice for progressive corneal ectasias. Although it has been described at length for keratoconus, there is little literature describing or advocating its use in PMD. In this article, we will review the evidence for CXL and its use in PMD.

Keywords: Cornea, Corneal collagen cross-linking, Pellucid marginal degeneration, Review article.

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INTRODUCTION

Pellucid marginal degeneration (PMD) is a rare progressive condition resulting in inferior corneal thinning and corneal distortion.[1] Alongside keratoconus and keratoglobus, it is considered one of the noninflammatory corneal ectasias. The focus of corneal thinning is greatest inferiorly and, in some cases, the central corneal thickness can remain unaffected.[1,2] Nevertheless, PMD is associated with a high degree of irregular astigmatism resulting in diminished visual acuity and overall reduction in visual quality. Traditional methods of treatment or disease management have been similar to those proposed for keratoconus; contact lenses, escalating to intrastromal rings, lamellar keratoplasty or penetrating keratoplasty.[1-5] In 1997, collagen cross-linking (CXL) was first described and has steadily gained acceptance as the treatment of choice for progressive corneal ectasias, such as keratoconus.[6,7] CXL, unlike other treatment modalities, is thought to address the underlying pathogenesis by strengthening the weakened connective tissue. The majority of evidence advocating the use of CXL has been centered around keratoconus, which is the commonest of the corneal ectasias. In this article, we will review the evidence for CXL and its use in PMD.

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PELLUCID MARGINAL DEGENERATION

Pellucid marginal degeneration is a bilateral, noninflammatory peripheral corneal ectasia resulting in inferior corneal thinning occurring 1 to 3 mm from the limbus in 4 to 8 o' clock positions.[1,8] The cornea superior to the area of thinning protrudes forward causing a 'beer belly' appearance, visible at the slit-lamp in its later stages.[1] Pellucid marginal degeneration presents typically between the ages of 20 and 40 years, with no sex predilection.[1] It causes reduced visual acuity due to high, irregular 'against-the-rule' astigmatism and is not associated with corneal vascularization, lipid or iron deposition.[1,9]

Pellucid marginal degeneration can be misdiagnosed as keratoconus and some researchers believe that the corneal ectasias (keratoconus, PMD and keratoglobus) represent different points on a spectrum of cornea thinning disorders rather than exist as different disease entities.[10-12] Walker et al used Scheimpflug imaging to demonstrate what are believed to be the hallmarks of PMD which include significant 'against-the-rule' astigmatism, marked peripheral corneal thinning near the limbus, relatively normal corneal thickness adjacent to the thinned area and a band of corneal thinning rather than a central or paracentral cone.[2]

The traditional management of PMD is similar to that for keratoconus. Often a stepwise approach is implemented commencing with rigid contact lenses, escalating to intrastromal rings, lamellar keratoplasty or penetrating keratoplasty.[1-5] Due to the location of the corneal thinning, the management in the later stages of the disease can be troublesome, as penetrating keratoplasty would be near the limbal edge and over a large area, and thus at greater risk of rejection. The traditional treatment methods

address the manifestations or consequences of the disease. Cross-linking, which has been used successfully to halt progression in keratoconus, offers the possibility of addressing the underlying problem that of corneal thinning and loss of corneal rigidity.

CORNEAL COLLAGEN CROSS-LINKING

Corneal CXL biomechanically strengthens the cornea through a photopolymerization reaction of riboflavin when exposed to ultraviolet-A (UVA) light resulting in increased covalent bonding of stromal collagen fibers.[6,13] The traditional settings are as per Dresden protocol and are 3 mW/cm^2 irradiance from 370 nm light source to illuminate a riboflavin treated eye for 30 minutes. This leads to a cumulative dose of 5.4 J/cm^2.[6,7]

Cross-linking has gained momentum as a treatment for keratoconus since its introduction 2003.[7] There have been several large and long-term studies demonstrating efficacy and safety. Raiskup-Wolf et al published 6 years follow-up results of 241 CXL treated eyes observing corneal flattening in 54% of cases, with a mean K_{max} reduction of –1.91 D.[14] This is in keeping with other studies that quote arresting disease progression in 97% of cases (52% disease stabilizing, 45% disease regression and 3% progression despite treatment).[15,16]

CROSS-LINKING FOR PMD

Although CXL has been described at length for keratoconus, there is little literature describing or advocating its use in PMD. This may be due the fact that PMD is less common than keratoconus but nevertheless, the literature available is confined to case reports and small case series rather than multicenter studies or randomized control trials.

In 2010, Spadea reported the successful use of CXL in the treatment of PMD in a 43-year-old female.[17] Traditional CXL was undertaken with a slight inferior decentration of the 9 mm treatment area but an untreated area 1 mm from the limbus was preserved. Visual acuity improved from 20/200 to 20/63 and remained stable for the follow-up interval of 12 months. Spadea also reported an overall astigmatic reduction of 1.40 D and reduction in apex power of 4 D.[17]

Kymionis et al first described the use of CXL combined with photorefractive keratectomy (PRK) treatment to both eyes in a 34-year-old woman with PMD.[18] Final best-corrected visual acuity (BCVA) measured at 12 months post-treatment was 20/25 and 20/32 in the right eye and left eye respectively compared to a preoperative visual acuity of count fingers in both eyes.[18]

In 2014, Kymionis et al presented the results of a prospective six patient (eight eye) series of PRK and CXL treatment for PMD.[19] No intraoperative or postoperative complications were observed. Visual acuity improved significantly post-treatment ($p = 0.018$) with mean preoperative BCVA of 1.05 (±0.33) LogMar and postoperative BCVA of 0.41 (±0.27) LogMAR.[19] Photorefractive keratectomy and CXL also had a significant ($p = 0.018$) effect on mean corneal astigmatism, which improved from –6.83 diopters (±2.33) preoperatively to –4.71 D (±1.89) postoperatively.[19] Patients in this series were monitored for a period of 12 months in which stability and improvement was sustained.[19]

In 2015, Bayraktar et al published a retrospective case series of two patients (four eyes) treated with CXL for PMD.[20] Three eyes were treated exclusively with CXL while one eye had CXL after intrastromal corneal ring implantation. Cross-linking was performed as per Dresden protocol with a 9 mm treatment zone, decentered inferiorly but respecting a 1 mm treatment free zone at the limbus.[20] Both patients had improvement in visual acuity and no reported complications. Mean apex power reduction was –0.35 D diopters, although there seemed to be an increase in apex power of –4.8 D in one eye, which may have affected the overall calculation.

An apprehension previously voiced about CXL and possibly more pertinent to the PMD patient rather than to the keratoconic, due to the location of corneal thinning, and hence site of CXL treatment, is that of limbal stem cell damage following CXL treatment.[21] Although the literature available for the use of CXL in PMD is limited, there were no reported cases of stem cell deficiency in the postoperative period or CXL-related patient complications.

CONCLUSION

The use of CXL for corneal ectasias and other ocular pathologies is increasing and with it a greater understanding of its potential uses, complications and its limits is emerging. The reported studies available for the use of CXL in PMD, albeit limited, are promising. Cross-linking was found to be safe, to halt ectasia progression and to stabilized or improve vision. More research is needed with greater patient numbers, longer follow-up periods and a multicenter participation to determine the scope of CXL in other corneal ectasias, such as PMD. It seems as though we are only seeing the tip of the Iceberg as we have yet to uncover the long-term effect of CXL on PMD and explore the effect of accelerated CXL. At present, the potential for CXL to treat most corneal ectasias seems endless and time will tell if we were right in our intuition.

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