OHTAC Recommendation

Collagen Cross-Linking Using Riboflavin and Ultraviolet-A for Corneal Thinning Disorders

November 2011

OHTAC Ontario Health Technology Advisory Committee

Background

The Ontario Health Technology Advisory Committee (OHTAC) met on June 24, 2011 to evaluate the effectiveness and safety of corneal collagen cross-linking using riboflavin and ultraviolet-A (CXL) for the treatment of corneal ecstasia (thinning disorders) following an evidence review by the Medical Advisory Secretariat (MAS).

The primary treatment objective of CXL is to halt the underlying disease progression, thereby delaying or deferring the need for a corneal transplant. It is currently the only treatment aimed at the underlying disease process.

Corneal Thinning Disorders

Corneal thinning disorders represent a range of disorders involving disease conditions such as keratoconus or corneal thinning occurring after refractive surgery. Keratoconus (KC) is the most common corneal thinning disorder. It is a rare disease (< 0.05% of the population) and is unique among major chronic eye diseases in that it has an early onset age (median age of 25).

Corneal thinning is a condition in which the normally dome-shaped cornea progressively thins, causing a cone-like bulge or forward protrusion in response to the normal pressure of the eye. This bulging can lead to an irregular corneal shape, resulting in a loss of visual acuity that can seriously impair an individual's ability to work or perform routine daily activities such as driving, television viewing, or reading.

Patients with KC are referred for corneal transplant as a last option when they can no longer tolerate contact lenses or when lenses no longer provide adequate visual correction. KC is one of the leading indications for corneal transplant and, despite high transplant success rates; there are reasons to defer the procedure for as long as possible. Patients with KC are generally young and life-long transplant survival duration would be necessary. Recovery after a transplant also involves lengthy time off work, potential complications from long-term steroid use following the surgery, and the risk of developing secondary cataracts, glaucoma etc. After transplant, recurrent KC is also possible with a need for subsequent interventions; residual refractive errors and astigmatism can remain challenging and high refractive surgery rates and re-graft rates have been reported.

Corneal Collagen Cross-Linking

Corneal collagen cross-linking involves the use of riboflavin (vitamin B_2) and ultraviolet-A radiation (UVA). A UVA irradiation device known as the CXL® device (license number 77989) by ACCUTECH Medical Technologies Inc has been licensed by Health Canada as a Class II device since 2008. The licensed indication by Health Canada for an illumination device that emits homogeneous UVA, in combination with any generic form of riboflavin, is to slow or stop the progression of corneal thinning.

UVA devices all use light-emitting diodes to generate UVA at a wavelength of 360-380 microns but vary in the number of diodes, focusing systems, working distance, beam diameter, beam uniformity and the extent to which the operator can vary the parameters. In Ontario, corneal collagen cross-linking is currently offered at over 15 private eye clinics by refractive surgeons and ophthalmologists.

The treatment is an outpatient procedure generally performed with topical anaesthesia and consists of several well-defined procedures. The epithelial cell layer in the central region is first removed and topical 0.1% riboflavin solution is then applied every 3 to 5 minutes for 25 minutes. A solid-state UVA light source with a defined wavelength and irradiance is used to irradiate the central cornea. Following treatment, a soft bandage lens is applied and prescriptions are given for oral pain medications,

preservative-free tears, anti-inflammatory drops and antibiotic eye drops. Patients are recalled 1 week postoperatively to evaluate healing and are followed up subsequently.

Not all KC patients are eligible candidates for CXL. For example, individuals primarily desiring to improve their vision are not suitable candidates. Treatment is considered for people with progressive disease who are contact lens intolerant, have adequate corneal thickness and are without central corneal scarring.

Evidence Review

A literature search was conducted on corneal collagen cross-linking with riboflavin (vitamin B_2) and ultraviolet-A (CXL) for the management of corneal thinning disorders using a search strategy with appropriate keywords and subject headings for CXL in literature published until April 17, 2011. The literature search for this Health Technology Assessment (HTA) review was performed using the Cochrane Library, ECRI and the Centre for Reviews and Dissemination database. The websites of several other health technology agencies were also reviewed, including the Canadian Agency for Drugs and Technologies in Health (CADTH) and the United Kingdom National Institute for Clinical Excellence (NICE). The databases searched included OVID MEDLINE, MEDLINE IN-Process and other Non-Indexed Citations such as EMBASE.

As the evidence review included an intervention for a rare condition, case series and case reports—particularly for complications and adverse events—were also reviewed. A total of 316 citations were identified and all abstracts were reviewed by a single reviewer for eligibility. For those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Findings

In the literature review by the Medical Advisory Secretariat, 65 reports (16 case reports) involving 1403 patients were identified involving the use of CXL for management of corneal thinning disorders. The reports were summarized according to their primary clinical indication, whether or not secondary interventions were used in conjunction with CXL (referred to as CXL-Plus), and whether or not it was a safety-related report.

The safety review was based on information from the cohort studies evaluating effectiveness, clinical studies evaluating safety or treatment response or recovery, and published case reports of complications. Complications such as infection and noninfectious keratitis (inflammatory response) reported in case reports generally occurred in the first week and were successfully treated with topical antibiotics and steroids. Other complications, such as the cytotoxic effects on the targeted corneal stroma, occurred as side effects of the photo-oxidative process generated by riboflavin and ultraviolet-A and were usually reversible.

The reports on treatment effectiveness involved 15 pre-post longitudinal cohort follow-up studies ranging from follow-up of only the treated eye, follow-up in both the treated and untreated fellow-eye, and follow-up in the treated eye and an untreated control group. One study was a 3-arm RCT involving 2 comparator groups; a sham treatment group with riboflavin only and the untreated fellow-eye.

The outcomes reported across the studies involved statistically significant and clinically relevant improvements in corneal topography and refraction after CXL. In addition, improvements in treated eyes were matched with worsening outcomes in the untreated fellow-eye. Improvements in corneal typography reported at 6 months were maintained at 1- and 2-year follow-up. Visual acuity, although not always

improved, was infrequently reported as vision loss. Additional procedures such as the use of intrastromal corneal ring segments, intraocular lenses and refractive surgical practices were reported to result in additional improvements in topography and visual acuity after CXL.

OHTAC Recommendations

Based on the above findings, OHTAC recommends the following with regard to corneal collagen cross-linking:

1. Based on moderate quality evidence that corneal collagen cross-linking effectively stabilizes the underlying disease process, OHTAC recommends that corneal collagen cross-linking be made available to patients with corneal thinning disorders such as keratoconus that are progressive in nature.
2. As corneal collagen cross-linking does not always improve visual acuity, adjunctive procedures such as intrastromal corneal ring segments, may need to be considered for visual rehabilitation and to avoid a corneal transplant.