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Corneal Collagen Cross-Linking in the Management of Keratoconus in Canada

A Cost-Effectiveness Analysis

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Purpose: To use patient-level microsimulation models to evaluate the comparative cost-effectiveness of early corneal cross-linking (CXL) and conventional management with penetrating keratoplasty (PKP) when indicated in managing keratoconus in Canada.

Design: Cost-utility analysis using individual-based, state–transition microsimulation models.

Participants: Simulated cohorts of 100 000 individuals with keratoconus who entered each treatment arm at 25 years of age. Fellow eyes were modeled separately. Simulated individuals lived up to a maximum of 110 years.

Methods: We developed 2 state–transition microsimulation models to reflect the natural history of keratoconus progression and the impact of conventional management with PKP versus CXL. We collected data from the published literature to inform model parameters. We used realistic parameters that maximized the potential costs and complications of CXL, while minimizing those associated with PKP. In each treatment arm, we allowed simulated individuals to move through health states in monthly cycles from diagnosis until death.

Main Outcome Measures: For each treatment strategy, we calculated the total cost and number of quality-adjusted life years (QALYs) gained. Costs were measured in Canadian dollars. Costs and QALYs were discounted at 5%, converting future costs and QALYs into present values. We used an incremental cost-effectiveness ratio (ICER = difference in lifetime costs/difference in lifetime health outcomes) to compare the cost-effectiveness of CXL versus conventional management with PKP.

Results: Lifetime costs and QALYs for CXL were estimated to be Can$5530 (Can$4512, discounted) and 50.12 QALYs (16.42 QALYs, discounted). Lifetime costs and QALYs for conventional management with PKP were Can$2675 (Can$1508, discounted) and 48.93 QALYs (16.09 QALYs, discounted). The discounted ICER comparing CXL to conventional management was Can$9090/QALY gained. Sensitivity analyses revealed that in general, parameter variations did not influence the cost-effectiveness of CXL.

Conclusions: CXL is cost-effective compared with conventional management with PKP in the treatment of keratoconus. Our ICER of Can$9090/QALY falls well below the range of Can$20 000 to Can$100 000/QALY and below US$50 000/QALY, thresholds generally used to evaluate the cost-effectiveness of health interventions in Canada and the United States. This study provides strong economic evidence for the cost-effectiveness of early CXL in keratoconus. *Ophthalmology 2017;■:1–12 © 2017 by the American Academy of Ophthalmology*

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Keratoconus is the most common primary corneal ectasia.[1] It is a progressive disease of bilateral asymmetric thinning and weakening of the cornea, resulting in myopia, irregular astigmatism, and central corneal scarring.[1] Keratoconus greatly affects quality of life through reduced visual acuity and visual quality.[2] In North America, keratoconus has a reported prevalence of 50 to 230 per 100 000 individuals and an incidence of 2 in 100 000 individuals.[3–5] It affects both genders and all ethnicities.[4] Typically diagnosed in puberty or early adulthood, keratoconus then can progress over the subsequent 10 to 20 years,[1,6] affecting young adults in their prime years of productivity.

Several treatment methods are used to manage keratoconus, depending on severity of disease. In early keratoconus, patients have been managed conventionally with spectacles and contact lenses. In up to 20% of cases, keratoconus progresses such that spectacles and contact lenses no longer provide adequate visual acuity or comfort, and corneal transplantation is considered.[3,5] Penetrating keratoplasty (PKP) is the most common form of corneal transplantation for keratoconus.[4,7] Penetrating keratoplasty has high success

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rates, along with potentially vision-threatening complications, including graft rejection and graft failure.[8] After PKP, patients undergo a lengthy recovery that requires frequent follow-up and prolonged use of topical medications, including antimicrobial and steroid drops. Deep anterior lamellar keratoplasty (DALK) is an alternative corneal transplantation technique with fewer reported complications, but data on long-term outcomes for keratoconus are limited.[7] Other surgical procedures used in keratoconus, including epikeratoplasty, photorefractive keratectomy, and intrastromal corneal ring segments, improve symptoms caused by refractive error,[4] but do not delay the underlying disease process. Among patients who have undergone transplantation, keratoconus may recur within the graft.[8]

Corneal collagen cross-linking (CXL) is the only available treatment that aims to halt the progression of keratoconus, thereby reducing the likelihood of vision loss.[2,9] Corneal CXL uses riboflavin and ultraviolet A light to enhance covalent bonding between collagen molecules in the cornea.[9] This results in increased corneal rigidity and enhanced resistance against proteolytic enzymes.[9] Introduced in human clinical studies in 2003, CXL is a relatively new, minimally invasive outpatient procedure that has few reported complications.[9] Early prevention of disease progression through CXL may help keratoconic patients to avoid corneal transplantation surgery and the associated costs, complications, and considerable follow-up care.

Corneal CXL recently received US Food and Drug Administration approval for use in the treatment of progressive keratoconus in the United States.[10] Evidence for the cost-effectiveness of CXL compared with conventional management of keratoconus is sparse. In the only known published study evaluating the cost-effectiveness of CXL in the United Kingdom National Health Service, Salmon et al[11] used a Markov cohort simulation model to compare 2 hypothetical cohorts of 1000 individuals with early keratoconus; one cohort underwent standard management, whereas the other underwent CXL around the time of diagnosis.

While Markov cohort modeling is commonly used in cost-effectiveness evaluations, patient-level microsimulation can be more powerful in reflecting disease progression and the impact of intervention. Microsimulation is a form of economic modeling that is particularly important when the patient's history (for example, time since disease onset) influences the likelihood of progression, costs, and health-related quality of life, as is the case in keratoconus.[12] While Markov cohort models apply the same time-fixed probability of moving between health states to all individuals in the cohort, microsimulation models allow for individuals to follow distinct pathways and transition between health states according to time-varying probabilities.[12] As individuals in microsimulation models move through time, their transition probabilities change. Thus, time-specific transition probabilities derived from existing studies that follow patients over their lifetimes can be applied. In comparison, in Markov cohort models, the entire cohort moves along the same trajectory, and the probability of transitioning between states does not change with time. Despite the higher data demands and greater computational burden, we believe that microsimulation can model keratoconus progression and the impact of intervention over time more accurately. The incidence of corneal transplantation is highly time dependent, with most occurring within the first 10 years after keratoconus diagnosis.[3] In addition, keratoconus tends to stabilize by the fourth decade of life, further reflecting the time-dependent nature of its progression.[4] The purpose of this study was to use patient-level microsimulation models to evaluate the cost-effectiveness of 2 potential treatment strategies for keratoconus in Canada: conventional management with PKP when indicated versus CXL.

Methods

Using R statistical software,[13] 2 state−transition microsimulation models were built in accordance with the International Society for Pharmacoeconomics and Outcomes Research best practices guidelines for state−transition modeling.[12] State−transition models conceptualize clinical situations as a set of mutually exclusive and collectively exhaustive states and transitions between states.[12] A modeled individual must be in only 1 state in any given cycle, but may move between states according to predefined transition probabilities. In each cycle, the individual incurs costs and obtains a health outcome associated with the state he or she is in. Individuals continue to cycle through the model until their death, which is determined based on population-based life expectancy tables. Cycle length should reflect the clinical problem, such that transitions can reflect the clinical context of disease and intervention effects.[12] For example, a disease requiring monthly postintervention follow-up, as is the case for keratoconus patients after corneal transplantation, must be modeled with cycles no longer than 1 month.

General Assumptions

We modeled keratoconus as a bilateral, asymmetric disease. Individuals were first diagnosed with keratoconus in both models at 25 years of age, the median age reported in previously published literature.[14] In the conventional management with PKP treatment model, we assumed that the second eye was diagnosed 5 years after the first.[15] In the CXL model, we assumed that both eyes underwent CXL shortly after the time of keratoconus diagnosis. Cycle lengths of 1 month were chosen to reflect preoperative and postoperative care. Each month, an individual could remain in his or her current state or move to a different one, the likelihood of which was determined by transition probabilities derived from available literature. Second eyes could follow different trajectories over an individual's lifetime. The maximum allowable age was 110 years. This ensured that our models reflected all possible lifetime costs associated with keratoconus and the impact of intervention. Throughout both models, we made realistic assumptions that minimized the costs and potential complications of PKP while maximizing the costs and potential complications of CXL. We strove to be conservative in our assumptions to avoid overestimating the potential benefits of CXL. We believe this to be important, given that CXL is a new technology with limited long-term outcome data.

Defining Health States: Conventional Management with Penetrating Keratoplasty Model

Figure 1 depicts health states relevant to keratoconus and the impact of conventional management with PKP on outcomes. Individuals in the conventional management with PKP model