2019 Health Technology Reassessment Report

Safety and Effectiveness Assessment of Corneal collagen cross-linking

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Summary (English)

▫ Assessment background

Corneal collagen cross-linking (CCXL) is a procedure that uses UV-A ray irradiation on the cornea for the purpose of strengthening the molecular bonds in the corneal parenchyma and preventing deformation of corneal shape in patients with keratoconus or iatrogenic corneal ectasia. This technology was notified by the name “corneal collagen cross-linking” as a result of new health technology assessment in 2010 (Ministry of Health and Welfare notification 2013-129, August 30, 2013).

The Ministry of Health and Welfare is in the process of converting 485 technologies that are non-benefit items into benefit items. This technology has already been assessed as a new health technology among the items to be decided by 2020. Accordingly, this health technology reassessment project (NR19-001, Principal investigator: In-Soon Choi) is being pursued to update the evidence for the safety and effectiveness of CCXL.

▫ Committee operation

The subcommittee consisting of a total of five members held a total of three subcommittee sessions over a 2-month period between May and July 2019.

▫ Assessment objectives and methods

Assessment was performed to determine whether CCXL is a safe and effective health technology for preventing deformation of corneal shape in patients with

keratoconus or iatrogenic corneal ectasia.

CCXL was compared to the untreated group for assessing its safety outcomes based on UV-induced corneal damage and procedure-related complications and effectiveness outcomes based on changes in corneal shape (keratometry, spherical equivalent, refractive cylinder, and corneal thickness) and vision (uncorrected visual acuity and best-corrected visual acuity).

For CCXL, five Korean databases, including KoreaMed, and foreign databases, including MEDLINE, EMBASE, and Cochrane Library, were used. A total of 3,400 articles were searched based on the search strategy, and after applying the selection and exclusion criteria, a total of 13 randomized clinical trials (RCTs) were included in the final assessment.

All steps, from article search, application of the selection criteria, to data extraction, were performed independently by the subcommittee and two assessors. Risk of bias was assessed using Cochrane's risk of bias, while the level of evidence was assessed using the GRADE method.

- **Assessment results and conclusions**

With respect to the safety of CCXL in patients with keratoconus, decrease in corneal endothelial cell density due to UV-induced corneal damage after the procedure was reported, but the subcommittee opined that the level of decrease was within the tolerance range with respect to the reproducibility of the endothelial cell test method. Other mild symptoms (corneal opacity, corneal edema, corneal erosion, inflammation, intraocular pressure, etc.) were reported as procedure-related complications, but it was

determined that these symptoms only appeared for a short period after the procedure and expected dissipate over time. Accordingly, the subcommittee assessed CCXL to be a relatively safe procedure for patients with keratoconus.

Meta-analysis on the effectiveness indicators, excluding uncorrected visual acuity, in patients with keratoconus showed that the CCXL group significant improvement in symptoms with decreased keratometry and improved best-corrected visual acuity, as compared to the control group. However, the results for keratometry measurements should be interpreted with caution since there was a high heterogeneity between the articles when the measurement point was less than three years. On the other hand, the amount of change in refractive cylinder actually increased in the intervention group to show no significant improvement. However, one study included in the meta-analysis had a study period of only one year and another study had a study period of three years, and thus, many more articles need to be reported to reach a conclusion about the effectiveness. The results for spherical equivalent and corneal thickness were not statistically significant, showing no improvement. Although naked vision was not included in the meta-analysis, three out of four articles that mentioned naked vision reported that naked vision improved more in the intervention group.

Analysis of CCXL in patients with iatrogenic corneal ectasia showed that, as compared to the control group, the CCXL group showed smaller keratometry, spherical equivalent close to 0, and higher LogMar letters measures for uncorrected visual acuity and corrected visual acuity to indicate that the symptoms were maintained or improved. However, the differences were not statistically significant. Considering that there was only one article, additional articles will be needed in the future to reach a conclusion about the effectiveness.

Analysis of CCXL in patients with keratoconus or iatrogenic corneal ectasia showed that the keratometry was smaller and corneal thickness was thicker after one year, as compared to three months after the procedure, which indicated that the symptoms were maintained or improved. With respect to vision, one article (Hersh et al., 2011) reported that naked vision logMAR in the intervention group improved more after one year than three months, while the other article (Greenstein et al., 2012) reported that improvement was confirmed based on decrease in LogMAR vision change. However, these indicators did not show statistically significant differences.

The CCXL subcommittee proposed the following based on the currently available assessment results.

CCXL could be considered a safe and effective technology for relieving symptoms by preventing deformation of corneal shape in patients with keratoconus. Moreover, this procedure has the advantage of being non-invasive, as compared to existing procedures, and is a health technology worth considering as an option for preventing the progression of keratoconus. However, the evidence for its use in patients with iatrogenic corneal ectasia was insufficient, and thus, more literature review would be necessary.

The Health Technology Reassessment Committee reviewed and determined that the findings of the subcommittee on CCXL are valid (September 20, 2019).