

# Corneal collagen cross-linking for keratoconus: Now data provide hint of benefit

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In patients with keratoconus the cornea of the eye begins to bulge. So-called corneal collagen cross-linking aims to halt this process. In this procedure, the cornea is stiffened through locally applied vitamin B2 in combination with UVA radiation. The German Institute for Quality and Efficiency in Health Care (IQWiG) investigated what advantages or disadvantages this procedure can have for patients and published its final report on 15 November.

Additional available [data](#) resulting from a query to the authors of an Australian study now show a hint of a benefit of corneal collagen cross-linking versus purely symptomatic treatment. But the data also provide a hint of harm. With regard to the comparison of different variants of the procedure with each other, the data only provide a hint of an advantage of the transepithelial procedure versus the conventional one. However, overall the evidence is still insufficient.

## Stiffening of tissue aims to halt progression

Keratoconus is a non-inflammatory tissue disorder of the cornea of the eye, typically already occurring in adolescents and young adults. The cornea begins to bulge, which may not only impair vision but, among other things, may also cause severe pain. In the advanced stage, corneal deformation can no longer be compensated with glasses or contact lenses; then the only option may be a corneal transplant.

Corneal collagen cross-linking is the first and so far only treatment option to halt the progression of corneal deformation in keratoconus. In the conventional procedure the cornea is mechanically exposed and treated with vitamin B2 (riboflavin) and UVA light, which aims to link the collagen fibrils, thus "stiffening" the cornea.

## **About a third of the studies cannot be used**

The Federal Joint Committee (G-BA) commissioned IQWiG to assess the benefit of this procedure compared with purely symptomatic treatment or with other types of corneal collagen cross-linking.

For the final report, IQWiG identified a total of 19 randomized controlled trials that are in principle suited to answer 1 of the 2 research questions. However, about a third of these studies could not be used. This was mainly due to the fact that the treatment results were not analysed in a manner appropriate to the respective study design.

## **Results could be biased**

In some studies only one eye of patients was randomly assigned to the treatment groups; in other studies, this applied to both eyes. Both study designs can be meaningful. However, if both eyes of a patient are considered in the study, then statistical tests or models have to be applied in the analysis to account for data dependency. But this was not the case, meaning the results could be biased.

## **Australian author group submitted IPD**

In principle, IQWiG can also conduct appropriate analyses post hoc. However, for this purpose further information on the studies as well as results data are required (individual patient data, IPD). The

corresponding requests to the study authors were initially unsuccessful - most author groups did not respond at all; some stated that they were not prepared to provide their data.

However, after publication of the preliminary report IQWiG was able to conclude a contract with an Australian study group, which regulates data use in detail. On the basis of IPD subsequently submitted to IQWiG, it was possible to consider this study in the assessment.

## **Advantage for uncorrected visual acuity, but also occurrence of side effects**

The results data of this author group show that, compared with purely symptomatic treatment, conventional corneal collagen cross-linking offers an advantage for vision. However, this applies only to "uncorrected [visual acuity](#)" (i.e. vision without corrective measures) not for "best-corrected visual acuity" (i.e. vision with corrective measures, e.g. by means of glasses).

In addition, the results on [side effects](#) are unfavourable for conventional corneal collagen cross-linking. This is because corneal haze and erosions occur more often than with purely symptomatic treatment. But this mainly refers to transient and reversible side effects.

IQWiG thus sees both a hint of benefit (uncorrected visual acuity) and harm (side effects) from treatment.

## **Vision better with transepithelial procedure**

For the second question, that is, the comparison of variants of corneal collagen cross-linking with each other, the data available showed relevant differences only between the transepithelial procedure and the

conventional one. Here, the data provide a hint of greater benefit of the transepithelial procedure for best-corrected visual acuity, but not for uncorrected visual acuity. In addition, a hint of lesser harm can be inferred from the study data, as the pain did not last as long after this procedure as it did after the conventional one.

However, it cannot be inferred from the data whether the transepithelial procedure also shows benefit or harm versus purely symptomatic treatment.

## **Further study results expected soon**

The data from the Australian study were robust enough to be considered in the analysis. However, the qualitative certainty of their results is still to be classified as moderate. And beyond this one study, the evidence is generally still unsatisfactory.

IQWiG thus recommends performing a conclusive assessment of corneal collagen cross-linking only when the results of completed but still unpublished studies or currently ongoing studies become available; IQWiG identified 26 such studies.

It is incomprehensible that some studies completed or discontinued some time ago have not been published - in part, this is not even intended. The picture that both researchers, as well as clinicians and patients, could obtain of corneal collagen cross-linking will thus in any event remain incomplete.

## **Process of report production**

IQWiG published the preliminary results in the form of the preliminary report in January 2016 and interested parties were invited to submit

comments. At the end of the commenting [procedure](#), the preliminary report was revised and sent as a final report to the commissioning agency in September 2016. The written comments submitted were published in a separate document together with the [final report](#). The report was produced in collaboration with external experts.

**More information:** [www.iqwig.de/en/projects-resul...eratoconus.6714.html](http://www.iqwig.de/en/projects-resul...eratoconus.6714.html)

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