College voor zorgverzekeringen

Report

Background report on assessing established medical science and medical practice for collagen cross-linking for keratoconus

ICD-10 code:
H18.6 Keratoconus

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Contents

Summary

Keratoconus is a progressive abnormality of the cornea, that can eventually necessitate corneal transplant. For some years collagen cross-linking (CXL) has been used in an attempt to terminate progression.
Proving the efficacy and safety of this treatment will require a longer period.

Several series and some comparative material can be found among the peer-reviewed literature which make a reasonable case for the efficacy and safety of CXL in the short term. Though there is little comparative material, the outcomes of the comparative material that does exist, and the many series, are consistent.

Nevertheless, there are too few clinical evaluations of sufficiently high quality and with a sufficiently long follow-up to be able to determine whether the effects will persist and whether no insurmountable disadvantages are associated with this treatment.
As a result, CXL does not comply with the “established medical science and medical practice” criterion.

1. Introduction

1.a. Reason

The SKGZ has asked for advice in relation to a dispute over the reimbursement of collagen cross-linking (CXL) for keratoconus. The matter of established medical science and medical practice in relation to CXL is pivotal to this dispute.

1.b. Background to keratoconus

Concepts

Keratoconus is a progressive, bilateral, usually asymmetric protrusion of the cornea. The diagnosis is usually made between the ages of ten and thirty. The degree of progression is variable and unpredictable. The reason for the diagnosis is usually astigmatic myopia that can eventually no longer be corrected with spectacles. It can also occur as a side effect resulting from laser-refraction treatment of the cornea, in which case it is referred to as keratectasia.

(Patho)physiology

The shape and clarity of the cornea are of vital importance for proper refraction and, as a result, effective visual acuity. Collagen is what maintains this shape. Collagen is supporting tissue that can be found throughout the body. Although a lack of strength in the collagen may play a role, the actual cause of keratoconus is generally unknown. A role may be played by atopia (allergy), with frequent rubbing of the eyes. Patients with the Down syndrome have a relatively high risk. Keratoconus is also associated with mitral valve prolapse, and a number of syndromes with more elaborate collagen-related problems: Marfan, Ehlers-Danlos and osteogenesis imperfecta. [1]

Prevalence

Keratonus is found in about 0.05% of the population [2,3]. It is not possible to determine exactly how many of these might be eligible for CXL, particularly because it is a new technique for which the indication parameters have not yet been fully crystallised.

Spontaneous course

Though the disorder is often progressive, the rapidity of the process is difficult to predict, and the severity and progression in the two eyes often differ. In the end, correction is often no longer possible, even with the most advanced and individually adjusted refractory aids, such as spectacles and lenses. There may be scarring on the surface of the cornea. Eventually, corneal transplant (or keratoplasty) may be necessary in order to retain or regain sufficient powers of vision. Without the possibility of stabilising the cornea,

eventually 20% will depend upon corneal transplant [1].

Standard treatment

Initially, correction is possible via spectacles, hard lenses, keratoconus lenses, or a combination of hard and soft lenses. When these no longer suffice, then corneal transplant may be unavoidable if the patient is to retain or regain proper eyesight.

Another technique used by some ophthalmologists is the placing of ring segments in the cornea (intracorneal ring segments, ICR). In their standpoint dated 4th March 2008, CVZ established that this technique has not been sufficiently evaluated and therefore did not comply with the Zvw-criterion "established medical science and medical practice".

New intervention

The new technique under discussion in this report is the so-called collagen cross-linking technique (CXL). This is intended to reinforce collagen tissue by artificially stimulating the formation of cross-links. The supportive and structure-giving properties of collagen molecules (long monomere chains) are based on their tendency to form connections with one another: "cross-linking". In applied chemistry, this process is known as: polymerisation.
The idea behind CXL is to halt progression at a stage in which correction via lenses is still possible.

Mode of action/technical construction

The mode of action is as follows. Under the influence of ultraviolet light (UV), riboflavin (vitamin B2) causes polymerisation, "cross-linking" of collagen.
During treatment, the epithelium of the cornea is first removed, then a riboflavin solution is applied and, lastly, the cornea is exposed to UV-radiation.

Indication problems

The indication should be made in cases of proven progressive keratoconus, but where it has not progressed too far. This is often already the case for children (young teenagers) with atopia, who rub their eyes excessively. Increasing short-sightedness (myopia) should put the ophthalmologist on the right track in time.

Potential risks

Potential short-term and long-term risks are:

- risk of infection (particularly with eye-rubbing, staphylococcal carriership)
- damage to the corneal endothelium
- early ageing of the cornea
- retinal damage
- corneal opacification/scarring.

1.c. Question to be answered by the literature study

Question

Has CXL, as treatment for keratoconus, been subjected to sufficient scientific evaluation and has it proven effective?
Is there sufficient evidence that, in the long term, CXL counteracts the progression of keratoconus sufficiently, so that the patient continues to benefit adequately from lenses?
Has its long-term safety been sufficiently demonstrated?

Relevant outcome measures

The following is important when choosing the outcome measures that are relevant within the framework of this literature study.

CXL is a technique that focuses on reinforcing the keratoconic cornea and preventing progression. This makes it possible to continue correcting the refractory problems with lenses, thereby avoiding corneal transplant.

In consultation with the external expert (section 5), we therefore examined the following outcome measures.

The most relevant final outcome measure is how often a corneal transplant can actually be avoided, or at least postponed for much longer, in comparison with patients who did not undergo CXL. No data on this could be found in the literature as the follow-up is too short, and hardly any comparative research of the different groups of patients has been done. See also section 3 on this subject, which describes the results of the search.

K-values

Another relevant outcome measure is the matter of whether CXL halts the progression of keratoconus. Relevant to this are outcomes that objectively measure the shape anomalies and the thickness of the cornea, and which provide facts and figures expressing the degree of progression or improvement. Many of these data are reported in the literature.
Almost all clinical studies reported the maximum, minimum or average K-values. K is the degree of convexity of the cornea expressed in dioptres (D). Keratoconus is characterised by large K-values and by a considerable difference in the maximum and minimum K-values. The K-max, K-min and K-average reflect the severity of the keratoconus.

Vision

Outcome measures such as the uncorrected and corrected visus are less important, in view of the goal of the treatment.

The degree to which CXL influences the clarity of the cornea is obviously important. If the corrected vision is greatly deteriorated as a result of CXL, then this should be regarded

as a complication. If the procedure causes vision to deteriorate by more than two Snellen lines, then the treatment was unsuccessful [4].

Chosen outcome measures

On the grounds of the above, keratometric outcome measures were therefore chosen, which almost all authors (also) reported as K-values. Attention was also paid to potential risks. The expert consulted (section 5) indicated that a 3-5 year follow-up is necessary in order to arrive at an adequate assessment.

2. Search strategy & selection of suitable studies

The aim of the literature search was to find as many peer-reviewed articles as possible containing data, based on patient material, relating to the effects of CXL for the indication keratoconus.

Search strategy

To this end, CVZ carried out a search on 12th April 2010, using the search terms Keratoconus AND (cross link* OR crosslink* OR CXL OR CCL OR riboflavin).

Databases & websites

The literature search was carried out in Medline, and the Cochrane Library over the period from when the databases were set up to 12th April 2010.

The websites of the following organisations were screened for standpoints issued on CXL for keratoconus: NICE, KCE, IQWIG, AETNA, CIGNA, HTAi.

The websites of the following organisations were screened for guidelines regarding keratoconus and CXL: Trip, National Guidelines Clearinghouse, GIN.

Selection criteria

Inclusion and exclusion of the articles found took place on the basis of abstracts. If articles could not be excluded on the basis of the abstract, then the whole article was examined.

The following were included:

- systematic reviews (table1)
- series found, comparative or not, that were not included in the reviews discussed (table 2)
- studies that are included in the reviews but which are worthy of separate discussion (table 2)
- studies that report on the safety of CXL (table 3)

3. Results

3.a. Results of the literature search

The 31 selected studies are presented in tables 1, 2 and 3.
The standpoints found are presented in appendix 2.
No relevant guidelines for this treatment were found.

3.b. Quality and assessment of the selected studies

Limited set-up

In general, the methodological set-up is limited: there is only one randomised comparative study, but this has not yet been completed. The published results are limited to only part of the patients who will eventually be included [3]. Furthermore, there are only series, which sometimes contain a comparative element. Within these methodological limitations, there are detailed reports on the effects. There is one comprehensive high-quality review [5] and one review of a lower quality [1].

A number of studies focus on determining the short-term risks and on finding risk factors.

A number of studies describe technical variations of CXL that depart from the standard CXL-technique.

The characteristics and results of the selected reviews and studies are presented in the tables.

3.c. Standpoints and guidelines

NICE review

The NICE is the only foreign package assessor to formulate a standpoint ("guidance") on CXL based on a comprehensive review of all the relevant literature they could find. The contents of that, in as far as relevant to the questions addressed in this report, are discussed in section 4, "discussion".

NICE standpoint

The NICE [6] concludes that there is still insufficient evidence on the safety and efficacy, both from the point of view of quality and quantity. As a result, they deem it only allowable under conditions of "clinical governance, consent and audit or research".

guidelines

No guidelines involving CXL can be found.

3.d. Efficacy

Table 1 Summary of articles: reviews

First author, Year of publication	Nature and contents of the review	Authors' conclusion	Comments	Ev Level [1]
NICE [6] 2009	Review based on a preliminary report of one RCT (ref 6), a non-randomised comparative study, four series, and collected case-reports. In addition the data of 17 series and case reports were also included in order to examine whether these would alter the conclusions of the other material.	The authors concluded that the literature found is inadequate with respect to quality and quantity. To be carried out by corneal experts and for audit and research only under condition of adequate determination of the indication.	Almost complete summary of literature available at that moment. This includes the following references from the CVZ search [3,7-18, 31]. See also the main text.	C High level
Ashwin[1] 2009	Publication based on the literature available. A systematic summary based on a series of at least 25 eyes. The results were analysed in order to draw conclusions on the efficacy.	Apparently, the longest follow-up (which varied from 4 to 36 months), supplies the clearest positive results.	Mainly a compilation of the results. Assessment of the results based on the largest series available. Included from the CVZ search: [2,3,7,9,11,13,18-20]. See also main text.	C modera te level

[1] As defined in the report "Assessment of established medical science and medical practice" (series no. 27071300):
A1: systematic review of at least two independently carried out A2-level studies;
A2: randomised double-blind comparative clinical research of a good quality and sufficient size (RCT);
B : comparative study, but without all of the characteristics of A2;
C : non-comparative research;
D : experts' opinions.
This classification applies to therapeutic interventions. Irrespective of the level, the evidence must have undergone peer-reviewed publication.

Table 2 Summary of articles: clinical studies alongside the reviews

First author, Year of publication	Type of research	Number of eyes/patients	Relevant outcome measures	Follow-up duration, Summary of results	Comments	Evidence class [1]
Wittig-Silva[3] 2008	Randomised comparative study	Treated Group: 33 eyes Contr. Group: 33 eyes	K-max	12 months. 1.45 +/- 1 D reduction in the K-max of the treatment group; 1.28 D (+/- ?) increase in the K-max of the control group.	Preliminary results, intake still going on. No further results published since then. No significance of the result is indicated between the groups.	B
Caporossi[21] 2010	"phase II study" Comparing results	44. Comparison with untreated eye in same patient	Average of K-max and K-min.	48-60 months, ave 52. Treatment group: reduc K-ave. treat. Group: 1.5 D. Inc. K-ave. contr group: 1. 5 D	part of a larger series, only that with a minimum of 48 months FU has been reported.	C/B
Coskunseven[22] 2009	Series, semi-comparative (crossover of ICR followed by CXL, poss. comparison with the contralateral eye)	Report does not clearly indicate number	K-average. SE ave. Cylinder.	12 – 14 months. First CXL gave better res. than first ICR	Due to combination of two techniques, no conclusion can be drawn over CXL as such.	None/C
Baumeister[23] 2009	Series	20 eyes of 20 pat.	Keratometric astigmatism	6 months. No increase in the keratometric values	Limited significance due to lack of data on the prior progression and the short FU.	C
Fournie[24] 2009	series	20 eyes, 20 pat.	Biomechanical stability (ORA), K-max.	3–18 months. ORA stable 83% stable or improved K-max.	Short FU. Unclear whether the missing 17% exhibited progression.	C
Goldich[25] 2010	series	14 eyes, 14 pat.	K-max, K-min. (harmful effects, see tab. 3)	12 months. Stable K-values	Study focused mainly on safety, see tab. 3	C

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A2: randomised double-blind comparative clinical study of a good quality and sufficient size (RCT);
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First author, Year of publication	Type of study,	Number of eyes	Relevant outcome measures	Follow-up duration, Summary of results	Comments	Evidence class [1]
Leccisotti[26] 2010	Series, semi-comparative	51 pat. Most severe eye received CXL, the other served as control	SE ave. Video-keratography Ave. Keratometry	SE: CXL red. 0.35 D, contr : incr. 0.83 D VK: CXL incr. 0.51D. contr: incr. 1.61 D GK: CXL red. 0.10 D, contr: incr. 0.88 D	Study into CXL without de-epithelialisation. The results seem poorer than with CXL with the usual de-epithelialisation.	C
Raiskup[27] 2010	Retrospective analysis Focuses on scarring complication	163 eyes, 127 pat.	K-average Scar formation, BCVA, UCVA Endothelium cell no.	FU 12 months. Analysis focused mainly on finding risk factors. See table 3	Focused on finding risk factors for scarring. Retrospective comparison of the keratometric starting values between the uncomplicated patients and the patients with post-CXL scars.	c
Koller[28] 2009	Series, semi-comparative	21eyes of 21 pat. Untreated eyes of the 21 pat. as control	Min. curvature radius, 7 different keratoconus-indices	FU 12 months. None of the treated eyes demonstrated progression. All untreated eyes did. Reduction of 4 of the 7 indices in the treated group (cornea became more regular shaped)	An important study due to its being semi-comparative, however with a limited FU duration.	B/C
Raiskup[4] 2009	Retrospective analysis Focused on complications: stromal haze.	163 eyes, 127 pat	K-average BCVA	FU 12 months. Analysis focused particularly on finding risk factors. See table 3	Focused on finding risk factors for stromal haze. Retrospective comparison of keratometric starting values between the uncomplicated patients and the patients with post-CXL stromal haze.	C

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Table 3 Summary of articles: studies focus on safety/complications

First author, Year of publication	Type of study	Eyes/patients	Assessed complications/failures	Results	Comments	Evidence class [1]
Raiskup[4] 2009	Retrospective analysis Focused on complication or failure	163 eyes, 127 pat.	Stromal haze (opacification of the cornea);	After 1 year 14/163 eyes had relevant stromal haze. The "haze" group had an ave. preoperative K of 71.1 D, the "clear" group had 62.1 D. (NS) The figures for the corneal thickness were respectively 478.1 mu en 420.0 mu (P=0.001)	Indications that the severity of the stage of the disorder increase the risk of opacification in the short term after CXL .	c
Raiskup[27] 2010	idem	idem	idem	idem	Double publication of the data of Raiskup 2009, in German, refers to scarring instead of opacification	c
Koppen[29] 2009	Case study of severe keratitis after CXL, from a large series.	117 eyes 4/117 keratitis	Postoperative keratitis	After 24 hours in 4/117 pat. Keratitis which responded well to topical corticosteroids. Permanent visus deterior. >2 Snellen lines: 2.8% in 2/4 keratitis patients.	Eventual failure/complicated CXL in 2/117 pat.	c
Koller[30] 2009	Series, registration of failure and complications.	117 eyes, 99 pat.	Visus deterioration, infiltrates, scarring and progression of the KC.	Sterile infiltrates: 7.6% Progression: 7.6% Risk of compl. seems to depend on old age or stage of the keratoconus.	Indications for only using CXL on keratoconus that is not too far advanced	c
Goldich[25] 2010	Series, registration of harmful effects on the cornea-endothelium and retina.	14 eyes	Endothelium loss Fovea damage	During regular follow-up, up to 12 months: stabile endothelium cell density and fovea-thickness.	No evidence of damage due to CXL	c

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4. Discussion

Long follow-up necessary

Treatment with CXL is intended to halt the progression of keratoconus at an early stage. It is impossible to predict whether a corneal transplant will eventually be necessary, and if so, when. This means that a proper assessment of its efficacy will necessitate a good follow-up lasting some years. The NICE-review [5] points out the theoretical danger than CXL could lead to increased ageing of the cornea, and that it is uncertain whether the procedure can or should be repeated after a number of years.

Comparative research necessary

The unpredictability of the progression, which even varies between the eyes of a given patient, makes it difficult to assess its efficacy adequately without a proper comparative study.

Reviews

In 2009 the NICE drew up a guideline based on the available literature. The comprehensive systematic review [6] of the NICE forms the basis to this background report. The inference of the report is that there is a lot of material that consistently points to promising results and – at least in the short term – that the progression of keratoconus can be halted without too many risks. The equally recent review of Ashwin is more limited, and included a limited number of studies without a clear indication of the inclusion and exclusion criteria used by the author. Neither is there a coherent conclusion, although the material he presented (which overlaps that of the NICE) is consistent with the NICE-conclusions (table 1).

Additional studies

The additional material found by CVZ also reinforces the probability of good efficacy in the short term. This material consists mainly of series, sometimes with a comparative element, for example in which a number of patients were treated in one eye and not in the other (table 2).

Complications

There were also a number of studies that focused specifically on researching failures or complications of CXL. These showed that the more advanced the keratoconus was, the greater was the risk of scarring. Similarly, a diminishing thickness of cornea increased the risk of complications. This means that only less severe cases with sufficient corneal thickness are eligible for CXL (table 3).

Modifications

Among the literature were also a number of articles that reported on technical modifications or combinations with other forms of treatment. For example, there is a study into CXL without de-epithelialisation [26], which is important because the study showed that the results with the usual de-epithelialisation turned out to be better. Furthermore, there is a small series in which a pouch was introduced into the cornea

with a femtosecond laser prior to riboflavin instillation [31] and one from the same author in which CXL was combined with photorefractive keratectomy (PRK) [32]. There is also a series in which CXL preceded or followed the placement of intracorneal ring segments ICR [22].
This study did not consider the results of studies into technical variations in the use of CXL.

Conclusion in relation to the effects of CXL

In the peer-reviewed literature we found many series and a certain amount of comparative material which make a case for the efficacy and safety of CXL in the short term. Though there is little comparative material, their outcomes, and the multitude of series, are consistent.
However, there is a lack of sufficiently high-quality clinical evaluations and a sufficiently long follow-up to be able to determine whether the effects will be permanent and whether this treatment does not have any insurmountable disadvantages.

5. Content-related consultation

For consultation on the contents, a draft of this report was presented to mr. M.J.W. Zaal, MD. PhD, ophthalmologist, academic medical specialist at the VU Medical Center and Chairman of the Cornea Working Group of the Dutch Ophthalmological Society (NOG). He agrees with its content and the use of the background reports. A number of additions were made to the draft text in response to his comments. He considers a follow-up lasting 3-5 years necessary in order to assess whether CXL has been successful. He also made a number of comments.

For example, he pointed out the possibility of using CXL as preliminary treatment prior to laser-refraction surgery. The cornea is sometimes too thin for laser treatment. In these cases, CXL prior to the laser treatment could provide the cornea with the necessary reinforcement. He feels that this possible broadening of the indication could lead to the unbridled use of CXL.

A very recent development that he mentioned is the combination of CXL with preliminary microwave corneal remodelling. This involves first using microwave energy to make the cornea flatter, after which the flatter cornea is strengthened by means of CXL.

CXL could be a solution for otherwise untreatable keratoconus, particularly in countries in which corneal transplant cannot be done due to the lack of possibilities for tissue and organ donation.

Mr. Zaal feels it would be a good idea to create possibilities – in the current phase of development of CXL – facilitating the experimental application of this treatment in specialised centres, under the condition of extra monitoring via, e.g., an endothelium camera.
He also advises the reassessment of established medical science and medical practice after a number of years.

6. Standpoint on established medical science and medical practice

standpoint	CXL does not fulfil the "established medical science and medical practice" criterion.
Evaluation necessary	Studies of sufficient size, (methodological) quality and follow-up duration are required in order to carry out a re-assessment.

7. Literature list

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33. College voor Zorgverzekeringen. Voorwaardelijke financiering in het kader van een verantwoord pakket. Diemen, 2009. Geraadpleegd in Juni 2010 via www.cvz.nl.

Appendix 1: Search strategy

On 12th April 2010, CVZ carried out a literature search using the search terms Keratoconus AND (cross link* OR crosslink* OR CXL OR CCL OR riboflavin).
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The literature search took place in Medline, and the Cochrane Library, over the period from when the databases commenced until 12th April 2010.

The websites of the following organisations were screened with regard to standpoint issued concerning CXL on keratoconus: NICE, KCE, IQWIG, AETNA, CIGNA, HTAi-VORTAL.

The websites of the following organisations were screened for guidelines on keratoconus and CXL: Trip, National Guidelines Clearinghouse.

Appendix 2: Summary of standpoints

Organisation	Description	Standpoint	Date
NICE [6]	Guidance	Accepted on the condition of “clinical governance, consent and audit or research”.	Nov. 2009.