



W Bruce Jackson

Bioengineered tissue onlay holds promise for refractive correction

By Cheryl Guttman
in London

LENTICULES fabricated from a tissue engineered corneal substitute material have the potential to be used as refractive onlays in a supplementary or alternative approach to laser-based refractive correction, reported W Bruce Jackson MD at the XXIV Congress of the ESCRS.

Dr Jackson described the technology being developed at the University of Ottawa Eye Institute and presented the case of the first human onlay implant procedure that was performed by Gustavo Tamayo, MD, of Bogota, Colombia.

"So far we have proven that it is possible to cleanly delaminate the epithelium and create a pocket on top of Bowman's membrane into which the onlay can be inserted, and we have seen that the epithelium heals rapidly over the onlay," said Dr Jackson, professor and chairman of ophthalmology, University of Ottawa, Ontario, Canada.

"Now we are continuing the clinical study by enrolling additional patients and will be gathering more information in longer term follow-up. There are many challenges ahead that will need to be addressed in the laboratory, but our experience so far is very encouraging."

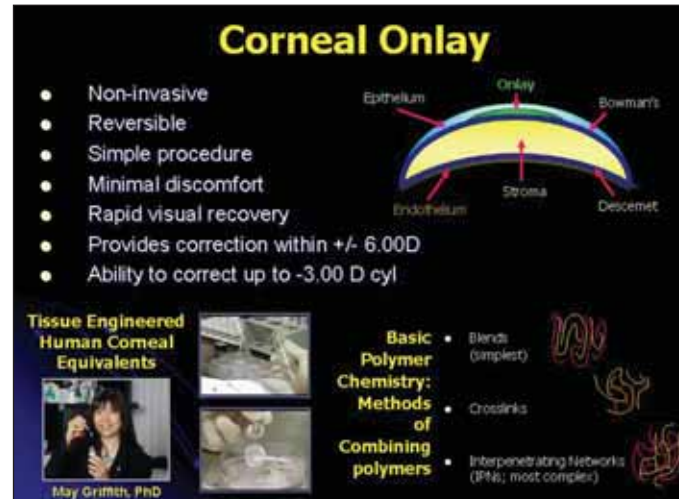
The first onlay implanted in a human eye was molded from cross-linked porcine collagen into a contact lens-like device. The material had a water content of 80 per cent to 90 per cent, measured 7.5mm in diameter with a central thickness of 70 microns, and featured a tapered edge.

"We expect the central thickness could range from 50 to 140 microns, which would allow corrections ranging from +6.0 to -6.0 D of sphere with up to -3.00 D of astigmatism. The tapered edge design is important to allow the epithelium to go over the onlay," Dr Jackson said.

In a collaborative effort with industry, the researchers worked with engineers at Gebauer to develop an instrument for creating a pocket for onlay insertion. The Gebauer Pocket Delaminator was designed as a modification of that company's EpiLase microkeratome (EpiLift).

"This device has been extremely reliable in creating a reproducibly sized 8.0mm diameter intact pocket. We would like to refine its performance so that the entrance to the pocket is narrower, but the experience with this early prototype has been very favourable," Dr Jackson said.

Histological evaluation including light and electron microscopic examination demonstrates the delaminator creates a very safe and clean separation. Bowman's membrane remains intact, the basement membrane is still attached to the epithelium, and there are no incursions into



the basal lamina or evidence of damage to the basal epithelial cell layer.

The first recipient of the corneal onlay was a 28-year-old female with keratoconus who was awaiting corneal transplantation. The onlay procedure was performed in the left eye that had a UCVA of count fingers, BCVA of 20/50, refraction of -3.00 -6.00 x 80, and keratometry of 51.00/55.00 x 150. Despite the steepness of the cornea, it was possible to create a clean pocket.

"That has not been the case in all eyes with a very steep K, but again we are only using eyes awaiting transplant for initial evaluation and they are not the population for which this procedure is intended. However, they will undergo corneal transplantation one to six months after the onlay procedure and so will offer the opportunity to evaluate these lenticules in situ," Dr Jackson said.

Tissue engineering a substitute cornea

The concept for this refractive surgery technique evolved from the research being conducted in the University of Ottawa research laboratory of May Griffith, PhD. Dr Griffith has been working to develop a tissue engineered corneal equivalent that could provide a physiologically functional substitute to human donor tissue.

"So, we posed the question of whether that material could be fashioned into a refractive onlay that would go under the epithelium and on top of Bowman's membrane. If successful, such an approach has many attractive features. The surgery would be simple and non-invasive, reversible, and provide rapid visual recovery with minimal discomfort," Dr Jackson said.

He added that although the current refractive correction research is targeting onlay development, it seems feasible that the lenticules could be placed into the

stroma under Bowman's membrane after creating a flap with a femtosecond laser.

The materials Dr Griffith has been developing are biosynthetic collagen-based polymers. Since synthesising the cross-linked porcine collagen used for the first human procedure, Dr Griffith and colleagues have gone on to create a cross-linked recombinant human collagen and are now focusing on synthetic interpenetrating networks (IPNs) of a synthetic material and a highly biocompatible collagen-based polymer.

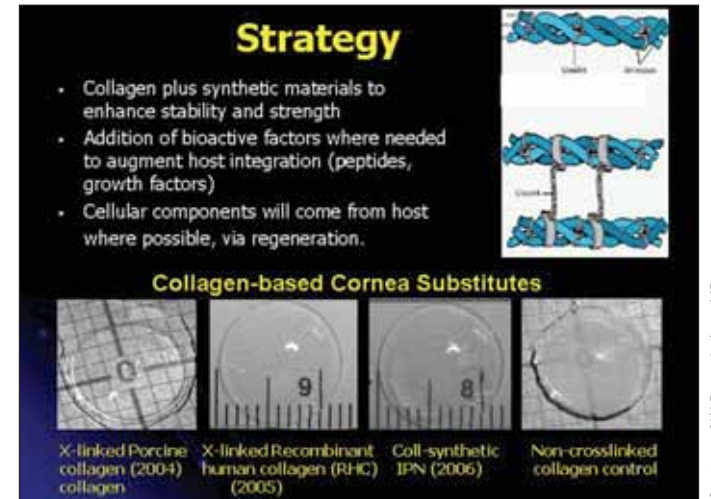
"The cross-linking procedure increases the stability and strength of the basic collagen polymer and makes it optically clear so that it is quite an improvement from the non-crosslinked collagens studied initially. The IPNs are even stronger," Dr Jackson said.

The porcine and recombinant human cross-linked collagens and synthetic IPNs that have been created all have biological properties mimicking those of the human cornea. For example, they all have a refractive index of 1.35, close to the 1.38 value of the human cornea. In addition they provide excellent transmission of white light and similar backscatter and glucose permeability compared with the human cornea.

"We would also like the materials to be ablatable, and all of those we've tested so far have been able to be lasered, even with the use of a femtosecond laser," Dr Jackson noted.

One drawback of the porcine cross-linked collagen was that it was relatively flimsy and so the very thin onlay used in the first human eye was somewhat difficult to manipulate during the insertion procedure.

"The cross-linked human recombinant collagen has more structure and can be handled with greater ease, and we are also working to develop a new insertion tool



for placing the lenticule into the pocket. However, we are still in the early stages of refining the techniques for handling and inserting the onlay," Dr Jackson said.

Additional challenges lie ahead

A variety of other issues also need to be addressed, including developing techniques for assuring proper centration of the onlay and its positional maintenance during the first few weeks during the epithelial healing process.

"The onlay seems to adhere very quickly, but I suspect there may be a layer of fluid within the pocket that might cause it to move. Therefore, we are looking at various bioactive peptides that will promote adherence of the onlay to the basement membrane as well as cytokines and growth factors that will stimulate wound healing and neurite ingrowth," Dr Jackson said.

Further research is also needed to achieve accurately powered lenticules and to investigate the long-term stability after insertion.

"Available follow-up from studies performed in a porcine model shows the bioengineered tissues are biocompatible and support healing and reinnervation. The material has remained optically clear for periods of at least 12 months, and both nerve ingrowth and the presence of hemidesmosome attachments has been observed.

Researchers at CooperVision, the University of Regensburg, Germany, and Linköping University, Sweden, are also part of the tissue engineering team, and the project has received financial support from the National Research Council of Canada.

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Courtesy of W Bruce Jackson MD