By Cheryl Gutman in London

BASED on the Helmholtz theory that cites age-related increase in crystalline lens stiffness as the underlying cause of presbyopia, investigators have been trying for many years to develop a technique for restoring near vision function by refilling the capsular bag with a deformable gel.

At the XXIV Congress of the ESCRS, Japanese ophthalmologist Okihiro Nishi MD described a novel lens refilling technique for restoring accommodation that utilizes a gel that polymerises after injection in the capsule.

Dr Nishi told attendees that leakage of the injected liquid material through the capsulorhexis opening prior to its polymerisation represents one of the greatest technical challenges investigators have faced in developing a successful lens refilling approach for treating presbyopia. To address that obstacle, Dr Nishi has developed a technique based on implantation of a dual-in-the-bag lens system.

The platform is comprised of a conventional foldable IOL, which is implanted posteriorly, and a piggybacked silicone accommodating IOL, which serves both as an optic and as a plug for sealing the continuous curvilinear capsulorhexis (CCC). The lens refilling material lies between the two IOls and is introduced via a small delivery hole in the haptic of the anterior IOL.

“Although numerous methods have been devised to address the problem of refilling material leakage, none so far has proven useful for possible clinical application,” explained Dr Nishi, Nishi Eye Hospital, Osaka, Japan.

“The principle for the dual lens approach is the same as the one I introduced about a decade ago with the invention of a silicone capsule sealing plug to prevent liquid silicone leakage. Preliminary testing to date in rabbit eyes is promising in demonstrating that this new refilling procedure is simple, safe and highly reproducible. We believe it represents a possible breakthrough in the development of a lens refilling technique and will begin testing it soon in primate eyes.”

Dr Nishi used a videotape presentation to demonstrate the surgical procedure as performed in a rabbit eye. It begins with creation of a 3.5mm central CCC and crystalline lens removal by phacoemulsification. Then, a conventional minus power IOL is implanted into the capsular bag.

“The implant used here has a sharp edge optic that will limit the development of posterior capsule opacification as the IOL compresses onto the posterior capsule,” Dr Nishi said.

Next, the accommodating IOL is implanted anteriorly and properly positioned using a Sinskey hook. The accommodating IOL is disc-shaped, has a 6.0mm optic with a plate haptic, and an overall length of 10.0mm.

After thoroughly aspirating the viscoelastic from the eye and with careful attention to removing it from between the two IOls, the Sinskey hook is used to pull aside the CCC edge for access to the gel-refilling hole. The injected material is a liquid silicone mix that polymerises in the eye within two hours.

Once the refilling is completed, the capsulorhexis edge is released and returns to its normal position, covering the delivery hole. Any small volume of silicone that leaks out as the capsulorhexis recovers can be aspirated out of the eye.

“It is really amazing that the accommodating IOL can seal such a large CCC opening to prevent silicone leakage. We believe it is because the polymer, which is cohesive and buoyant, causes the accommodating IOL to press from the inside against the capsulorhexis,” Dr Nishi said.

“The ability of the system to avoid leakage was investigated in a porcine cadaver eye model in which force was applied to the globe. No leakage occurred when the IOL was pushed centrally. Only when continuous, excessive force was applied from an eccentric direction was a small amount of silicone leakage observed.

“However, the leakage could be readily identified and removed by aspiration, and there was no further leakage in the absence of continued force applied to the lens,” Dr Nishi said.

**Modelling the perfect refillable lens**

Researchers from Advanced Medical Optics (AMO), Groningen, The Netherlands, presented their findings from studies using theoretical and animal models to investigate accommodation achieved after lens refilling.

Henk A Weeber MSc, biophysics research scientist at AMO Groningen BV, The N.etherlands, and colleagues have undertaken theoretical studies in a mechanical computer model to explore the accommodative amplitude that can potentially be achieved by lens refilling and how it is influenced by surgical and material variables.

“The goal of these studies is to gather information about what outcomes are attainable in the ideal situation before advancing into in vivo testing,” said Dr Weeber.

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In constructing the model for these investigations, the researchers used published data on lens geometry from Dubbelman et al., which had been derived from Scheimpflug images taken in human subjects at different states of accommodation. The base input for the model represented the average shape of the lens at its maximum accommodated state.

Data on the mechanical properties of the natural lens for designing the model came from previous studies conducted by Dr Weeber and colleagues in which they defined the local stiffness within the lens.

Then, the performance of the model was tested by comparing its predicted changes in lens power and surface radii with accommodation with measurements derived from in vivo Scheimpflug images obtained in a single human subject.

Comparisons were also made between the model-derived data and in vitro stretching experiments incorporating lens refilling using materials of varying stiffness.

“The model performed well in both of these tests and so we were confident about its validity,” Dr Weeber said.

Determinations of the amount of accommodation that could be achieved were based on the assumption of exchanging the natural lens with 100 per cent volume of a soft material that would polymerise or cross-link in vivo. One simulation determined how the accommodative amplitude achieved might vary if the lens was in its fully accommodated versus fully disaccommodated state at the time of refilling. The refilling volume was assumed to be the same for both situations.

When the lens was first stretched to its full disaccommodated state, the crystalline lens removed, and the capsular bag refilled, the accommodative amplitude was reduced by about 22 per cent relative to the natural lens, from 4.6 D to 3.6 D.

“This finding is consistent with observations in animal experiments where a decrease in accommodative amplitude occurred after lens refilling. Nevertheless, the magnitude of accommodative amplitude achieved is still sufficient to be functional,” Dr Weeber said.

In this simulation, it was also observed that even after 100 per cent refilling, the lens shape changed and became thinner.

“This alters the lens power in the disaccommodated state, but emmetropia can be achieved by adjusting the refractive
injectable lenses,” he commented. It may be possible to restore human biocompatibility and accommodation research and development, AMO Thom Terwee PhD, manager of biophysics, preclinical studies More encouraging results in firming attached to the capsule. per cent less than when the polymer is accommodative amplitude was up to 50 freely along the capsule, the achieved transmission of forces from the zonule to disaccommodation, making the capsule, the capsule was sliding along the adherence between the polymer and the capsule, the capsule was firmly attached to the capsule, the capsule was sliding along the adherence between the polymer and the capsule, the capsule was firmly attached to the capsule. The findings from these studies suggest it may be possible to restore human accommodation to a functional level with injectable lenses,” he commented. Part of the biocompatibility research has focused on developing an effective treatment protocol for inhibiting proliferation of lens epithelial cells (LECs) as that phenomenon would hinder the success of a refilling procedure for restoring accommodation. Initial studies were conducted in vitro in cell cultures and ex vivo in porcine cadaver eyes. Based on the findings in those models, the research advanced into in vivo testing in rabbit eyes. In the living animals, the crystalline lens was removed and a viscoelastic solution containing demineralised water, cycloheximide, and actinomycin was injected into the capsular bag and left in place for five minutes prior to lens refilling. Eyes treated with that approach have remained essentially clear for at least 12 months and still exhibit only minimal opacification at 16 months, Dr Terwee reported. “We were amazed by these outcomes considering that after routine lens removal without any capsular treatment, rabbit eyes develop significant opacification within just a few months,” he noted. Pre-presbyopic, adolescent rhesus monkeys were used in studies to determine accommodation amplitude achieved after lens capsule filling procedure. In those experiments, accommodation was stimulated pharmacologically using pilocarpine or carbachol iontophoresis. A Hartinger coincidence refractometer was used to measure refraction before and after stimulation, and accommodative amplitude was calculated as the difference between those values. “This measurement provides an objective determination of the accommodative optical change in power and also gives an indication of the overall optical quality of the refilled eye based on whether or not it is possible to measure the refraction,” noted Dr Terwee. The surgical technique involved performance of a complete iridectomy several weeks prior to lens refilling to prevent miosis and enable measurement of refraction during pharmacologically-stimulated accommodation. Removal of the natural lens nucleus and cortex was performed through a small 1-2 mm capsulorhexis in the periphery, and after the LEC treatment, the capsulorhexis was closed with a silicone plug and the capsular bag refilled. The material used for lens refilling was a two-component silicone polymer that becomes crosslinked in the eye in a temperature-dependent reaction. It offers optical and mechanical properties that mimic the crystalline lens of a 20-year old eye. “This material is optically clear, has a refractive index of 1.43, and a low Young's modulus,” Dr Terwee said. Postoperatively, animals were treated with topical medications to prevent inflammation that would also interfere with the ability to measure refraction. Some eyes were treated only for postoperative inflammation and did not receive the LEC treatment. In those eyes, opacification developed quickly and it was not possible to measure refraction and determine accommodative amplitude,” Dr Terwee said. Results from eyes that were exposed to the LEC treatment prior to refilling showed that technique was less effective than in the rabbits for preventing opacification, although it delayed LEC proliferation to the extent that it was possible to measure accommodation over a period of many months. “We are hoping to be able to improve the LEC treatment so that it is more effective in delaying opacification,” Dr Terwee said. The results from the refraction measurements showed that the injectable polymer capsular filling lens concept was capable of creating an accommodating lens. Accommodation was measured in nine eyes after pharmacologic stimulation. Mean accommodation achieved after surgery was 4 D and decreased to about 2.5 D over time. “The responses among the eyes were variable both initially and over time. Some eyes achieved only a minimum amount of accommodation, and in some eyes the accommodation essentially disappeared during follow-up, whereas in others the responses were stable for longer. In my mind, however, the most important result is the maximum accommodative amplitude achieved, which was 6.5 D initially after the surgery and remained at 4.5 D after nine months. That response suggests this technique has the potential to be successful for restoring functional accommodation,” Dr Terwee said.