

## Ultrasound Circular Cyclo-Coagulation – Innovation in Glaucoma with High Intensity Focused Ultrasound

A report on the satellite symposium 'UC<sup>3</sup>, One Giant Step in Glaucoma with High Intensity Focused Ultrasound' held at the World Glaucoma Congress, 30 June 2011, Paris

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### Abstract

Existing treatment modalities for glaucoma, including pharmacological therapy, lasers, surgery and shunts, are all associated with shortcomings. Ultrasonic coagulation of the ciliary body with pinpoint precision using high intensity focused ultrasound (HIFU) enables significant reduction of aqueous inflow and intraocular pressure (IOP). Energy is focused through non-optically transparent media with controlled energy absorption, reducing effects on adjacent tissues. Energy deposition and tissue heating at the focus site do not depend on tissue pigmentation, thus improving predictability. Currently, high-frequency miniaturised transducers create small focal zones for improved treatment area targeting, and ultrasound focusing provides enhanced control. The high operating frequency allows a sharp transition between the focal zone and the untreated area, reducing risks of heating adjacent healthy tissue. Such transducers are used extensively in malignant tumour treatments. Novel Ultrasound Circular Cyclo-Coagulation (UC<sup>3</sup>) with a miniaturised annular transducer uses HIFU technology. The circular geometry of the device allows precise, constant and reproducible positioning. Results from animal studies and from a clinical pilot study of patients with refractory glaucoma indicate that ultrasonic coagulation of the ciliary body using HIFU delivered by a circular miniaturised transducer is an effective and well-tolerated method of reducing IOP. The single-step procedure is short, easy to perform and accurate. Glaucoma impacts patients' quality of life, including unpleasant treatment side effects and social and physical aspects. Gold-standard trabeculectomy shortcomings highlight the need for precise, focused surgical modalities. HIFU is a non-invasive, cost-effective innovation that, should the multicentre clinical trial demonstrate similar results to the preclinical and pilot studies, will be a useful addition to current glaucoma management techniques.

### Keywords

Ciliary body, glaucoma, high intensity focused ultrasound (HIFU), intraocular pressure, cyclophotocoagulation, trabeculectomy, Ultrasound Circular Cyclo-Coagulation (UC<sup>3</sup>)

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## High Intensity Focused Ultrasound for Glaucoma

A report on a presentation by Shlomo Melamed<sup>1</sup> and Eric Sellem<sup>2</sup>

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In spite of many existing therapies, refractory glaucoma continues to be an unsolved challenge. According to the World Health Organisation, glaucoma is the second most common cause of blindness worldwide, with approximately 67 million patients affected.<sup>1</sup> The proportion of patients who do not respond to medical treatment ranges from 30–50%.<sup>2,3</sup>

Apart from eye drops and surgery, another therapy used to treat refractory glaucoma is ciliary body destruction. Several energy sources and different techniques for destroying ciliary body processes have been studied by researchers. These include diathermy, cryotherapy, diode or neodymium-doped yttrium aluminium garnet (Nd:YAG) laser and ultrasound via the transscleral route,<sup>4-7</sup> transpupillary cyclophotocoagulation<sup>8</sup> and intraocular endophotocoagulation.<sup>9</sup>

The conventional clinical treatment is diode laser transscleral cyclophotocoagulation, comprising partially destroying ciliary body

processes and reducing production of aqueous humour and intraocular pressure.<sup>10-12</sup> However, laser cyclophotocoagulation has low selectivity for ciliary body processes and, although effective, is not well tolerated. Destruction of surrounding tissue causes complications, such as hypotony, phthisis, hyphaema, scleromalacia, uveal reactions, ocular pain and discomfort, and ocular inflammation followed by vision loss, and repeated sessions are required. Laser cyclophotocoagulation is currently reserved for cases of patients with highly advanced glaucoma and poor vision.<sup>13-18</sup> ■

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## High Intensity Focused Ultrasound – Technology That May Change Surgery

A report on a presentation by Gail ter Haar

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Early clinical and preclinical trials of ultrasonic coagulation of the ciliary body using high intensity focused ultrasound (HIFU) demonstrated that cyclodestruction using this method is effective in lowering high intraocular pressure (IOP).<sup>5,19</sup> In a multicentre trial of therapeutic ultrasound for glaucoma where treatments were performed on 880 eyes, the one-year multi-treatment success rate was 79.3% when retreatment was used following treatment failure.<sup>20</sup> A clinical series performed with the commercial SonoCare™ Therapeutic Ultrasound System Model demonstrated that this process was effective in reducing IOP.<sup>21-23</sup>

A benefit of ultrasound over laser is that the energy can be focused through non-optically transparent media to produce controlled thermocoagulation, without the effects of explosive disruption on surrounding tissue. Ultrasound effects are predictable, since tissue heating and energy deposition at the focus are independent of pigmentation quantity, a variable parameter in the ciliary body. Focused ultrasound can be used to treat tissue volumes at any site or depth in the eye.<sup>24</sup>

Despite the efficacy of HIFU, its use for ciliary body destruction was abandoned in the mid-1990s, partly due to the bulky design of the commercial system and relative complexity of the process. The distance of the large transducer from the eye had to be measured. Each HIFU exposure created a single pinpoint lesion. The transducer then required moving for each of the approximately six lesions. Thus the process was complex and slow.

Furthermore, two types of complications were observed with the early ultrasound technique: those associated with poor placement, and those related to an excessive tissue response. If the focus of the beam was incorrectly positioned on the sclera or if the patient moved, lesioning placement errors resulted. Complications from an excess tissue response included severe iritis and hypotony.<sup>25-27</sup>

HIFU can now be carried out using miniaturised transducers, which produce small focal regions and give improved targeting and control of therapy zones, especially in small organs such as the ciliary body. More complex transducers allow the creation of lesions of variable geometry, which can be used to treat hard-to-access tumours. The risk of heating adjacent healthy tissues is small, because there is a steep temperature gradient between the focal region and its surroundings. Three-dimensional modelling of the magnitude and shape of the desired necrotic volume results in a minimisation of the energy required.<sup>28-30</sup>

Focused ultrasound transducers are used for many different medical treatments, as it is possible to use focused ultrasound beams in a minimally invasive procedure to target selective deep-seated masses such as malignant tumours. Magnetic resonance imaging-guided HIFU devices have been used for extracorporeal treatment of uterine fibroids,<sup>31-33</sup> while HIFU with ultrasound guidance has been used in cancer and for transrectal therapy of the prostate.<sup>34</sup> ■

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## Glaucoma – From a Patient's Perspective

A report on a presentation by David Wright

*International Glaucoma Association, London*

In an ideal situation, glaucoma is diagnosed before the symptoms are apparent, and the disease is explained to patients so that any fears they may have can be addressed. Patients worry about ultimate blindness, fear falls and a decline in their overall health condition, and are apprehensive regarding their possible involvement in motor vehicle accidents, restrictions to driving and subsequent inability to work in

particular occupations. However, if it is diagnosed early, glaucoma can be treated before it has had a significant impact on patients' quality of life and they can retain useful sight for life.<sup>35-39</sup>

As patients generally do not report symptoms until advanced damage has occurred, glaucoma is usually detected at a late stage,

when the condition is already symptomatic. The disease is explained to a greater or lesser extent and treated, but there can be issues with patient behaviour towards compliance, adherence to treatment and effectiveness, leading to further loss of vision. Issues that can affect patients’ compliance with their eye drop treatment include perceived benefits, tolerability of adverse side effects, comfort, ease of use and frequency of application. Depending on when the diagnosis was made, there may be a significant loss of vision within patients’ lifetime.<sup>38-47</sup> Sometimes, because of the late stage of the condition, there is a significant impact on quality of life both from the treatment and the condition, and a significant loss of vision within patients’ lifetime.<sup>38,42,48</sup>

is no longer sufficient, laser treatment may be offered. Surgery with pharmacological augmentation is offered to patients with advanced glaucoma who are at risk of progressing to sight loss despite treatment.<sup>49</sup> Medical treatments have disadvantages: poor tolerance due to adverse side effects, difficulty in instilling the eye drops and lack of compliance, which all impact on patients’ quality of life. Lasers and surgery are associated with risks and a significant fear factor, which again affect patients’ quality of life and, although these treatments are effective for a certain time, how long their effect is sustained is disputed. The greatest negative effect on quality of life is when patients lose their driving licences, sometimes long before there is a noticeable visual loss from their perspective.<sup>50-52</sup>

The current UK treatment regimen recommends first-line treatment with prostaglandin analogue or prostamide eye drops for patients newly diagnosed with early or moderate chronic open-angle glaucoma. When this treatment is insufficient to stabilise the disease, further medication is added to the patients’ regimens. Once medical treatment

The ideal scenario for the management of glaucoma is when it is detected early, controlled without the use of eye drops or invasive techniques, and an effective, safe treatment is available in the long term. In that way, the loss of patients’ driving licence can be prevented and significant impact on quality of life avoided.<sup>38,42,50</sup> ■

## Ultrasound Circular Cyclo-Coagulation – From Theory to Therapy

A report on a presentation by Florent Aptel

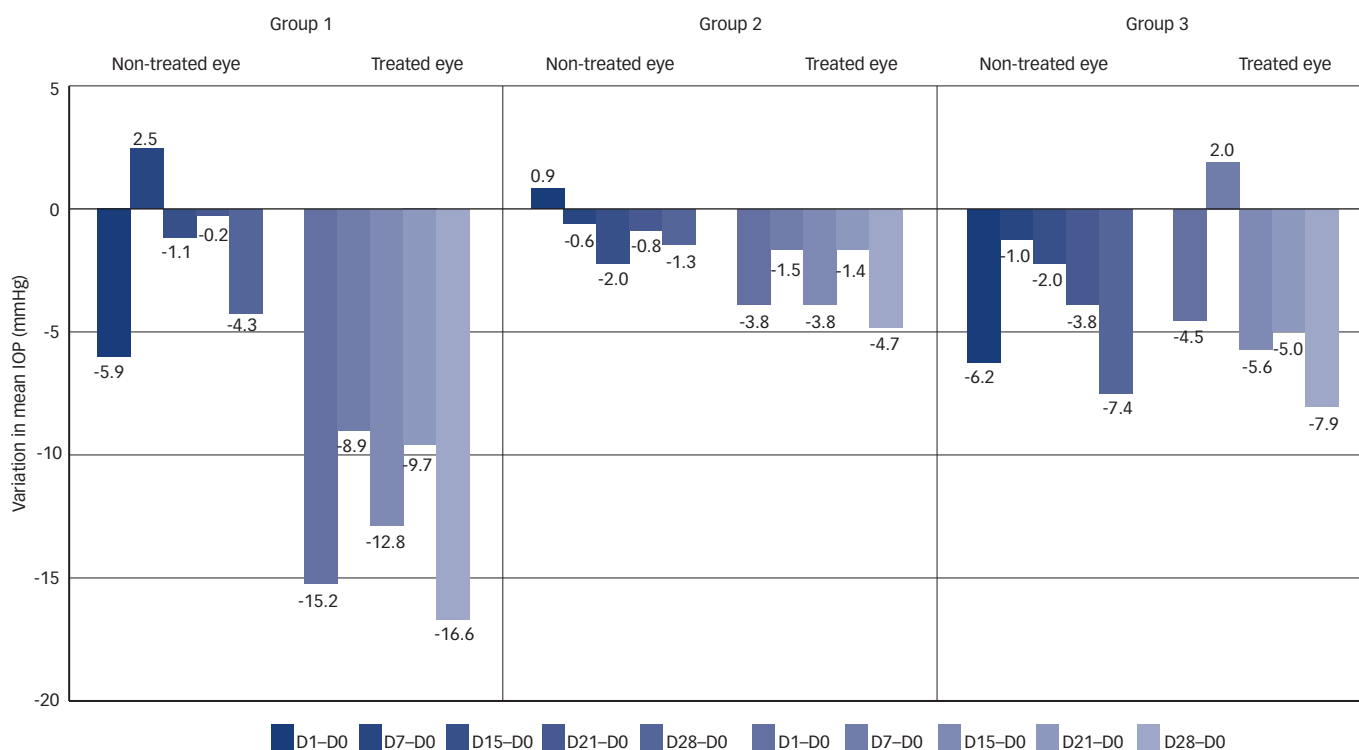
Edouard Herriot Hospital, Lyon

A study to develop a novel miniaturised device that allows safe, rapid and easy treatment of glaucoma using high intensity focused ultrasound (HIFU) cyclocoagulation was undertaken to create a one-step, accurate procedure allowing the whole circumference of the ciliary body to be treated. The strategy adopted, Ultrasound

Circular Cyclo-Coagulation (UC<sup>3</sup>), capitalises on the circular symmetry of the eyeball to treat the ciliary body.

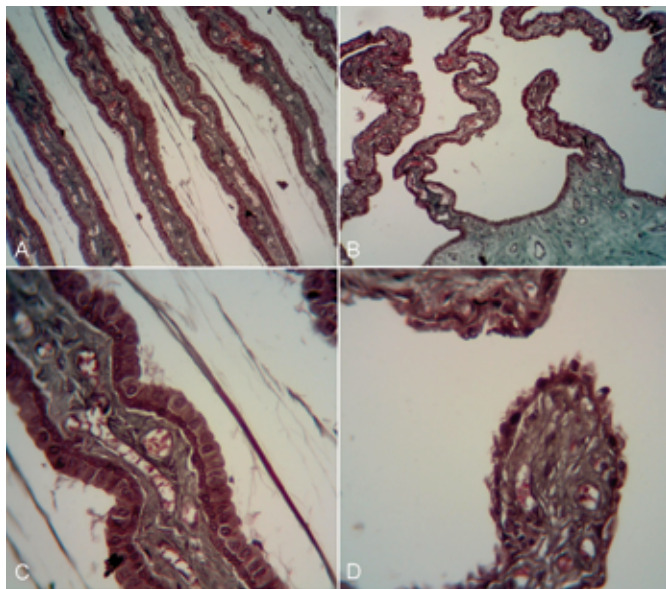
The device did not exceed the dimensions of the eye and treatment conformed to the ciliary body. The circular geometry of the device

**Figure 1: Variations in Mean Intraocular Pressure in Treated and Non-treated Eyes between Different Days Post-treatment and Day 0 of Treatment with Ultrasound Circular Cyclo-Coagulation**



IOP = intraocular pressure.

**Figure 2: High-magnification Photomicrographs Showing Ciliary Processes with Coagulation Necrosis, Loss of the Bilayered Epithelium and Vascular Depletion of the Stroma (B, D) and Undamaged Ciliary Processes (A, C)**



allowed reproducible and constant positioning. To create six line-focus beams, the device was divided into six separate cylindrical transducers. The probe was attached to the eye using a truncated cone filled with saline solution. The prototype was designed using numerical simulations, which allowed adjustment of exposure conditions and operating frequency of the device to reduce thermal injury to the ciliary body. The prototype was produced, acoustically characterised and tested in thermosensitive gel and *in vivo*.<sup>53</sup>

Numerical simulations were performed with suitable transducer geometry. Theoretical thermal lesions were positioned only within the ciliary body processes by modifying three parameters:

- acoustic intensity;
- exposure duration (time on); and
- pause between exposures (time off).

Using the miniaturised device, the possibility of positioning the focus of six ultrasonic beams in a circle at the required depth

was demonstrated on an acoustic pressure map. The position of the six focal lines was consistent with the theoretical location. To control the placement of lesions, tests on thermosensitive gels were performed. The treatment angle in gel was compliant with theoretical transducer positioning on the device. *In vivo* experiments on rabbits demonstrated significant intraocular pressure (IOP) reduction. The histological section showed conformal treatment of the ciliary body without side effects.<sup>53</sup>

To evaluate the histological effects and clinical outcomes of HIFU delivered by miniaturised annular transducers for ciliary body coagulation in an animal study, 18 eyes of 18 rabbits were insonified using a six-sector transducer ring. Six sectors were activated in six rabbits (group 1), five sectors were activated in six rabbits (group 2) and four sectors were activated in six rabbits (group 3).<sup>54,55</sup>

The IOP on day 28 after treatment was significantly reduced ( $p < 0.05$ ) compared with the IOP before treatment (day 0) in all three groups of treated eyes. IOP reduction at day 28 was significantly greater in the treated eyes of groups 1 and 2 ( $p < 0.05$ ), but not in group 3, compared with non-treated eyes. IOP reduction was significantly greater in the treated eyes of group 1 compared with those of groups 2 and 3 ( $p < 0.01$ ) at all time points (see *Figure 1*). No macroscopic abnormalities of the eyes were observed post-treatment. No abnormalities were observed during anterior segment and fundus examination on post-treatment days one and 15. Histological changes were circumferentially dispersed on the ciliary processes. The intermediate and distal parts of the ciliary processes in the affected areas revealed acute inflammatory and necrotic changes ranging from stromal oedema and vascular congestion to coagulation necrosis with loss of surface epithelium and haemorrhage; however, the basal part of the ciliary body appeared normal (see *Figure 2*). The inflammatory cellular reaction measured by the presence of giant cells, polymorphonuclear or plasma cells, lymphocytes or macrophages was very limited.<sup>54,55</sup>

HIFU delivered by circular miniaturised transducers in rabbit eyes produced localised, reproducible and sustainable histological lesions of the ciliary processes and did not damage surrounding ocular tissues. The single-step procedure was short – lasting one minute – easy and accurate. UC<sup>3</sup> of the ciliary body using HIFU was an effective and well-tolerated method of reducing IOP in an animal study.<sup>54,55</sup> ■

## EyeOP1® Device – First Outcomes of Human Trials

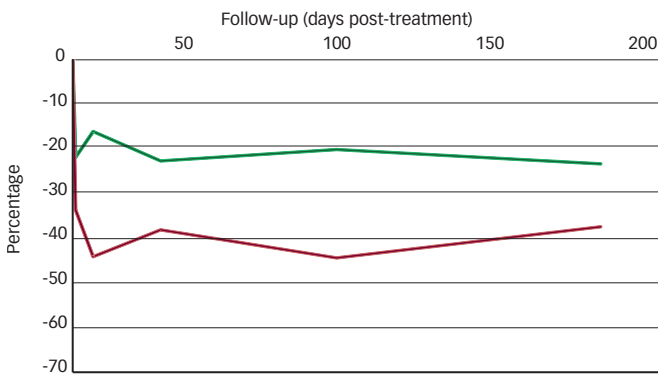
A report on a presentation by Philippe Denis

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The first pilot study evaluating the safety and efficacy of high intensity focused ultrasound (HIFU) delivered by miniaturised annular transducers in patients with refractory glaucoma was approved by the French National Health Regulatory Authority in the light of preclinical study results. In this prospective, non-comparative, interventional clinical study using the EyeOP1® Device (EyeTechCare), 12 eyes of 12 patients with glaucoma and uncontrolled intraocular pressure (IOP) were insonified using a ring comprising a six-sector

transducer. Due to the high transducer operating frequency (21 MHz), at which energy absorption is high, the total amount of energy required to be delivered to the eye was low. Ultrasound biomicroscopy (UBM) and complete ophthalmic examination were conducted before the procedure and one day, one week, one month, three months and six months afterwards. The following parameters were used: duration of each shot three seconds (group 1, patients 1–4) or four seconds (group 2, patients 5–12).<sup>56,57</sup>

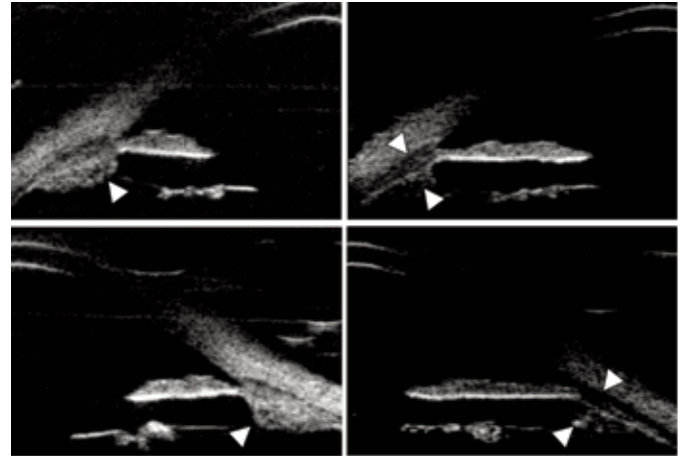
**Figure 3: Relative Intraocular Pressure Reduction from Baseline in Group 1 (Green) and Group 2 (Red)**



In group 1, IOP was reduced from a mean pre-operative value of  $35.6 \pm 2.5$  mmHg (n=2.2 glaucoma medications) to a mean post-operative value of  $27.9 \pm 5.7$  (n=2.2),  $29.6 \pm 4.9$  (n=2.2),  $27.3 \pm 3.2$  (n=3.0),  $27.8 \pm 9.0$  (n=2.7) and  $27.0 \pm 4.9$  (n=2.5) at one day, one week, one month, three months and six months, respectively. In group 2, IOP was reduced from a mean pre-operative value of  $39.1 \pm 13.2$  mmHg (n=4) to a mean post-operative value of  $26.9 \pm 15.1$  (n=4),  $23.0 \pm 13.1$  (n=4),  $24.2 \pm 9.2$  (n=4.2),  $23.1 \pm 10.6$  (n=4) and  $25.4 \pm 6.2$  (n=3.4) (see Figure 3).<sup>56,57</sup>

No major intra- or post-operative complications occurred. Superficial punctate keratitis occurred in three patients and central superficial corneal ulceration in one patient. All these patients presented with a pre-operative pathological condition of the cornea. UBM demonstrated

**Figure 4: Ultrasound Biomicroscopy Showing Ciliary Body and Ciliary Processes before (Left) and 30 Days after (Right) Ultrasonic Circular Cyclo-Coagulation (Aviso® 50 MHz Probe, Quantel Medical)**



localised and reproducible cystic involution of the ciliary body in eight of the 12 eyes, no damage to the surrounding ocular tissues and a suprachoroidal fluid space in six of the 12 eyes (see Figure 4).<sup>56,57</sup> Circular coagulation of the ciliary body using HIFU delivered by a ring-shaped miniaturised transducer is an effective and well-tolerated method of reducing IOP in patients with refractory glaucoma. The single-step procedure was short (less than two minutes long), easy and accurate.<sup>56,57</sup> ■

## How Technology Can Improve the Standard of Care in Glaucoma Surgery

A report on a presentation by Tarek Shaarawy

*Glaucoma Unit, University Hospitals of Geneva*

The gold-standard glaucoma treatment, trabeculectomy, is associated with many shortcomings, including high complication rates and extensive post-operative follow-up – clinicians must consider post-operative management to be of equal importance to the surgical procedure itself.<sup>58</sup> Evidence suggests that deep sclerectomy may offer a favourable alternative to trabeculectomy.<sup>59,60</sup> Most studies report significantly lower early post-operative complications compared with trabeculectomy. However, the randomised controlled trials comparing deep sclerectomy with trabeculectomy are not conclusive when it comes to efficacy.<sup>61-65</sup>

Tube shunt implants have been retained for patients at high risk of failure with trabeculectomy and patients who had previously failed trabeculectomy. However, these implants remain labour-intensive and could be associated with serious complications.<sup>66</sup>

Severe loss of central vision has been documented to occur in 6 % of eyes post-trabeculectomy in advanced glaucoma cases.<sup>67</sup> Other complications that commonly occur include hypotonic maculopathy and inflammation.<sup>68</sup> Cataract incidence post-trabeculectomy, beside its damaging effect on vision, requires another intra-operative surgery, which could adversely affect initial trabeculectomy results.<sup>69</sup>

The efficiency of surgery may be overemphasised compared with the need for safety. Most surgeons choose to postpone surgery,<sup>70</sup> due to the possible vision risk complications of classic trabeculectomy, until the late stages of glaucoma.<sup>67,68</sup> There is an unmet need for predictability in surgery, which demonstrates a decline in its outcomes over time.<sup>71</sup> Furthermore, surgery does not meet the need for speed to maximise the utilisation of limited resources.<sup>72</sup>

Canaloplasty may be a safer alternative to trabeculectomy; however, its extensive use is hindered by its surgical difficulty, which results in long learning curves. It is difficult to use en masse surgical treatment due to technical complexity. Another drawback is that all non-penetrating glaucoma surgery does not appear to reach its predefined target intraocular pressure in a significant percentage of cases without the post-operative utilisation of goniopuncture, which requires access to laser equipment.<sup>73</sup> Laser-assisted surgery used to perform deep scleral dissection in deep sclerectomy is promising, but we still lack knowledge about its medium- to long-term success rate,<sup>74</sup> as well as there being a marked lack of trials associated with economic assessment in glaucoma.<sup>72</sup> Research into stents would be useful to increase long-term success rates.<sup>75</sup> Trabecular micro-bypass stent surgery may meet the need for rapid implantation procedures.<sup>76</sup>

## Discussion

Data from the preclinical and pilot clinical trials provide strong evidence that the novel and groundbreaking Ultrasound Circular Cyclo-Coagulation (UC<sup>3</sup>) technique conducted with the miniaturised high intensity focused ultrasound (HIFU) device represents a major innovation in the treatment of glaucoma. HIFU delivered by circular miniaturised transducers produced localised, reproducible and sustainable histological damage of the ciliary processes and did not damage the surrounding ocular tissues. Circular coagulation of the ciliary body using HIFU is an effective and well-tolerated method of reducing intraocular pressure (IOP) in patients with refractory glaucoma. The single-step procedure was short (less than two minutes), easy and accurate. This novel development of HIFU for the treatment of glaucoma is an effective technique that is likely to be a particularly useful addition to the current armamentarium of glaucoma management techniques.

## Future Developments

The EyeMUST multicentre clinical study will evaluate the effectiveness and safety of glaucoma treatment by UC<sup>3</sup> using HIFU with the EyeOP1® Device (EyeTechCare). EyeMUST will involve

approximately 20 international centres and is set to commence during the fourth quarter of 2011.

The first centres in France will be set up in nine departments of university-affiliated and private practice hospitals: University Hospitals of Dijon and Lille; Quinze-Vingts (two departments), Saint Joseph and Val de Grâce Hospitals in Paris; Croix-Rousse and Edouard Herriot Hospitals and Kléber Centre, Private Hospital Clinique du Parc in Lyon. The international centres will be located in Germany, Israel, Italy, Spain, Switzerland and the UK.

The Conformité Européenne (CE) certification, obtained to market the EyeOP1 device designed as a novel therapeutic solution for glaucoma, allows the launch to markets in Europe and in countries outside Europe accepting this label. If the EyeMUST multicentre clinical trial results, estimated to be available in late 2012, show similar results to those already demonstrated in the pilot study, UC<sup>3</sup> with HIFU will be a most valuable supplement to the current range of glaucoma treatments. In future, widespread use of this totally non-invasive and cost-effective technique is likely to have a profound effect on the prognosis of many glaucoma patients. ■

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