EURO TIMES
Supplement
Dec 2015/Jan 2016

# Oraya Therapy for Wet AMD, Real World Clinical Outcomes

Saturday 19 September 2015
15th EURETINA Congress
Nice, France

# Introduction

Age-related macular degeneration (AMD) affects an estimated 30 million to 50 million people worldwide and is the leading cause of severe vision loss in higher income countries.

Neovascular AMD accounts for about 10 per cent of AMD cases, but for about 90 per cent of the severe vision loss that AMD causes. It affects approximately 1.3 per cent of people over 50 years old, with approximately 600,000 new cases of neovascular AMD diagnosed annually.

Throughout the early years of this century, there has been a succession of new treatments for neovascular AMD, each improving on the last, starting with photodynamic therapy (PDT) with verteporfin (Visudyne®, Bausch & Lomb), followed by anti-VEGF agents like pegaptanib sodium (Macugen®, Bausch & Lomb), ranibizumab (Lucentis®, Novartis), and aflibercept (Eyelea®).

Each step along the way has been greeted with great enthusiasm by retinal specialists, followed by some discouragement with the realisation of the limitations of the treatments and controversies regarding their cost.

In the case of PDT, there is a stabilisation of vision but no significant visual improvement and the treatment has to be repeated every three months. Moreover, it requires patients to stay out of the sun and wear dark sunglasses for a couple of days.

Pegaptanib sodium administered intravitreally is much easier for the patient, but like PDT, it does not improve vision and has to be injected repeatedly to maintain its effect. It was soon displaced by agents like bevacizumab and ranibizumab, which actually improved vision but still require repeated injections.

All of those treatments are very expensive and justifying their use to insurance companies and public health systems has not always been easy. The fact that the treatments have to be repeated not only increases their expense but can be inconvenient for patients. Moreover, the repeated puncturing of the eyeball poses the risk of a range of complications, including a small but significant risk of that most dreaded of complications, endophthalmitis.

Results from the INTREPID study show that, in eyes with neovascular AMD, a single treatment of stereotactic radiotherapy with the Oraya Therapy can significantly reduce intravitreal injections over two years of follow-up while maintaining vision

Stereotactic radiotherapy with the IRay® Radiotherapy System (Oraya) is aimed at reducing the need for repeated anti-VEGF injections in people with neovascular AMD. Building on decades of research on the effect of radiation therapy on the submacular vasculature, it is intended as a one-time treatment to selectively halt the progression of the neovascular membrane.

The components of the IRay® Radiotherapy System include a low-energy X-ray Tube that produces a narrow, highly collimated beam, the I-Guide™ Eye Stabilization Device, to stabilise and align the eye for accurate delivery of X-ray at the retinal lesions. The I-Guide also includes optical reflectors that work with the beam positioning system to enable precise localisation and tracking of the eye.

Results from the *INTREPID* study show that, in eyes with neovascular AMD, a single treatment of stereotactic radiotherapy with the Oraya Therapy can significantly reduce intravitreal injections over two years of follow-up while maintaining vision.

At a *EuroTimes* Educational Symposium held at the 15th EURETINA Congress in Nice, France, a panel of retinal specialists and a radiation oncologist met to discuss the theoretical basis of the treatment, as well as its real-world clinical results as a second- and first-line treatment for neovascular AMD.

# The Need to Reduce Injection Frequency

**Tim Jackson PhD, FRCOphth | t.jackson1@nhs.net**

Moderator Tim Jackson PhD, FRCOphth, King's College Hospital, London, UK, introduced the symposium by highlighting the strain that repeated injections put on both patients and those who treat them. Anti-VEGF agents can produce very good results, but the need for repeated hospital visits can have its own impact on patients' quality of life and on the resources of healthcare systems. Stereotactic radiotherapy with the Oraya device may help reduce that burden and help with capacity issues, and reduce the sheer effort patients need to go through.

"I'm very keen on any technology that reduces the number of injections that patients may need while maintaining vision as well as possible," Dr Jackson said.

# Oraya Therapy in Neovascular AMD, its Mechanisms and Synergy with Anti-VEGF

**Frank Zimmermann MD | frank.zimmermann@usb.ch**

Radiation oncologist Frank Zimmermann MD, University Hospital Basel, Switzerland, shared his insights on the effect of radiation therapy on brain, vascular structures, and especially the eye, the types of results achieved in trials using earlier technology and the aim of combining the treatment with anti-VEGF treatment.

Studies involving the radiation treatment of brain tumours have shown that the dominant effect with doses beyond 12 Gy as a single fraction is vascular damage and that single doses of 16 Gy or higher have a relevant vascular effect, completely obliterate arteriovenous malformations (AVMs) in 80 per cent of cases. However, stereotactic treatment technique has to be conducted with perfect precision and high knowledge to avoid severe late toxicity as necrosis to the brain or of other structures.

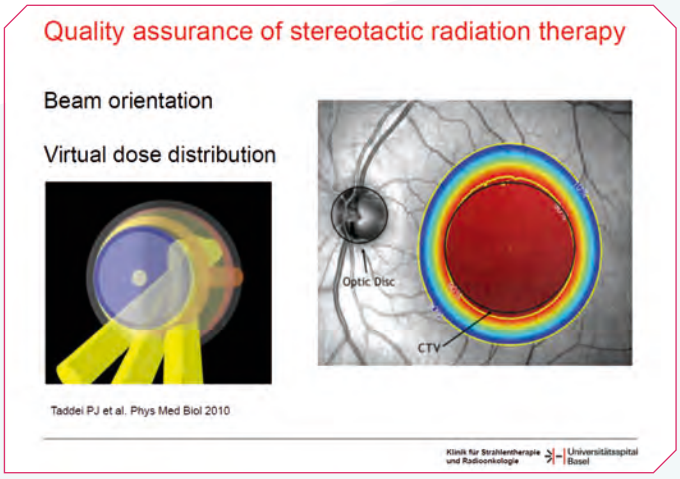
Results of studies with radiation therapy in AMD conducted in the late 1990s and early 2000s have been somewhat controversial, because of the conflicts of interpretation arising from differences in the techniques used, the different means of evaluating efficacy, and the different populations treated.

Fractionation schedules varied considerably between the studies, with some investigators using single doses of 1 Gy to 4 Gy only, with about 10 to 20 Gy total dose. Dividing the dose in this way causes completely different biological effect with only a minor effect on the vascular system.

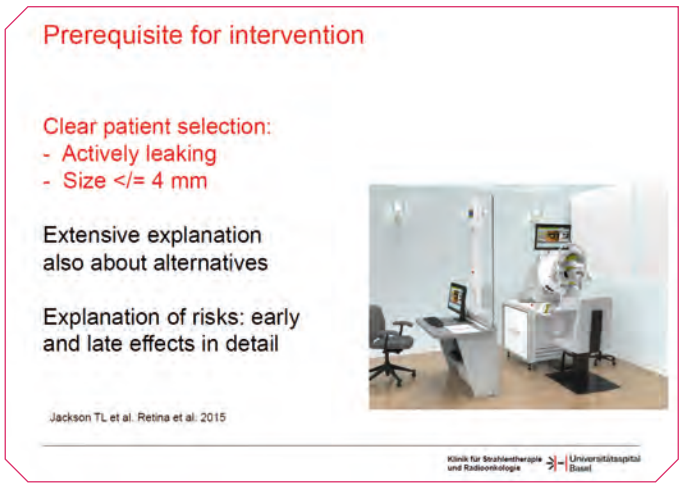
The old trials showed a small but not significant advantage for radiation therapy, which may have sometimes been influenced by bias because not all of the randomised trials have been double-blind and they had a fairly short follow-up. However, it can be concluded from the studies on AMD and other vascular diseases that the optimal effect against the vascular system is achieved through the application of one fraction with about 16 Gy within about a few minutes of treatment.

The studies showed that when radiation therapy is applied in this way there is a regression and inactivation of subretinal neovascularisation, a re-absorption of fluid and blood and a reduction in leakage and bleeding from the abnormal vascularisation. Moreover, after six to 24 months there is subretinal fibrosis and vascular obliteration which is the ultimate aim of the treatment in AMD.

On the other hand, the trials have also shown that with doses greater than 20 Gy there is mild retinopathy with loss of photoreceptors and pigment epithelial atrophy in 15 per cent of the treated eyes (*R Trikha et al, Retina 2011; 31:13015-1311*). For that reason, high precision and a very steep dose gradient are mandatory.




*Precise targeting and steep dose fall-off using Oraya Therapy*




*Proper patient selection and advice is necessary*

## WHY THE NEED FOR RADIATION THERAPY?

Prof Zimmermann noted that the *EXCITE* study has demonstrated that AMD will progress if the interval between anti-VEGF injections after the first year of treatment is proactively increased to three months without any other auxiliary treatment (*U Schmidt Erfurth et al, Ophthalmology 2010;118:831-839*). The aim of radiation therapy is to provide a one-time treatment that will reduce the number of injections patients need over time and still maintain their visual gains.

The Oraya Therapy device uses three external low-energy (100kVp) X-rays to deliver a radiation dose of 16 Gy to the macula with sub-millimetre precision. The system includes an eye stabilising device, the I-Guide, a camera and screen to verify and control the aim of the beam. It also has an exact robust and reproducible patient positioning apparatus to further enhance beam navigation.

## EARLY RESULTS PROMISING

So far, Oraya Therapy has been shown to be safe and effective, provided the lesions are small and the radiation dosage is adequate. And although the longer term consequences beyond 3 years are not yet known, it is important to remember that intravitreal injections have their own side effects, including conjunctival haemorrhage, eye pain, increased intraocular pressure (IOP) and retinal haemorrhage.

With appropriate and cooperative patients, macular degeneration is resolved in a noteworthy number of patients already within about six to 12 months after administration of Oraya Therapy, Prof Zimmermann said, although the effect will very likely persist longer. The time to effectivity is due to the effect of radiation on the abnormal vasculature related to the cell division cycle and the time for resorption of the fluid. It is then possible to increase the treatment interval of injection of anti-VEGF.

The predictability and safety of the treatment have been confirmed in eyes with axial lengths from 20mm to 26mm. The current recommendation is to exclude patients with axial lengths less than 20.0mm and more than 26.0mm, in order to stay safely within those margins.

The size of the lesion that can be safely and effectively treated is 4.0mm or less, because of the size of the beams used and also to avoid damage to the optic nerve.

Regarding safety, quality assurance testing of stereotactic radiotherapy using modern algorithms of dose distribution

shows that the treatment will deliver negligible doses (<0.7 Gy) to the optic disc, the optic nerve, the lens and the cornea (*PJ Taddei et al, Phys Med Biol 2010;55:7037-7054*).

Prof Zimmermann emphasised the importance of providing patients undergoing Oraya Therapy with an extensive explanation regarding all the different options in their situation. Patients also need to be aware of the potential risk involved, because the longest follow-up with the treatment is as yet only three years. But at the moment it is the most precise system of its kind and the older trials have shown that radiation doses of 16 Gy are not causing severe side effects, but documented only for a limited follow-up period and after fractionated concepts.

In summary, he noted that stereotactic radiotherapy with the Oraya system has a strong biological efficacy and a close interaction with anti-VEGF treatment. The two treatments have a synergistic effect, and since they are aimed at the same target, both the amount of radiation therapy and the amount of anti-VEGF injections necessary to achieve the desired effect are lower.

> This system has very high precision... and it is a very comfortable, non-invasive treatment for patients, being conducted in 30 to 60 minutes

"This system has very high precision, which is essential, and it is a very comfortable, non-invasive treatment for patients, being conducted in 30 to 60 minutes. The reduced need for anti-VEGF injections is also highly appreciated by patients, if you ask them after 12 months or 24 months," he added.

# Integration of Oraya Therapy as a Second Line Therapy

**Mahdy Ranjbar MD | mahdy.ranjbar@uksh.de**

Oraya Therapy was granted a CE mark in 2010, and there are now a number of centres offering the treatment in three European Countries, Germany, Switzerland and the UK. Mahdy Ranjbar MD, University of Lübeck, Germany, presented the six and 12-month results of the first patients treated at his centre.

Dr Ranjbar noted that the number of patients with neovascular AMD is huge and ever-growing. In Germany, for example, there are 30,000 new cases of AMD diagnosed every year. So far only anti-VEGF has been shown to be able to significantly improve the vision of patients with the disease. Its effect is rapid but short-lasting, and therefore, to maintain their visual acuity, patients require many injections over a lifetime.

However, clinical experience shows that, over time, patients tire of the repeated injections and they can also have difficulty making their appointments for a variety of reasons. As a result, patients are often undertreated, or discontinue their treatment entirely, and their condition worsens and the gains achieved in visual acuity are lost.

"We need to maximise the visual outcome and minimise the risk of long-term scarring and also, from a socioeconomic point of view, we need to reduce the financial burden of repeated injections," Dr Ranjbar said.

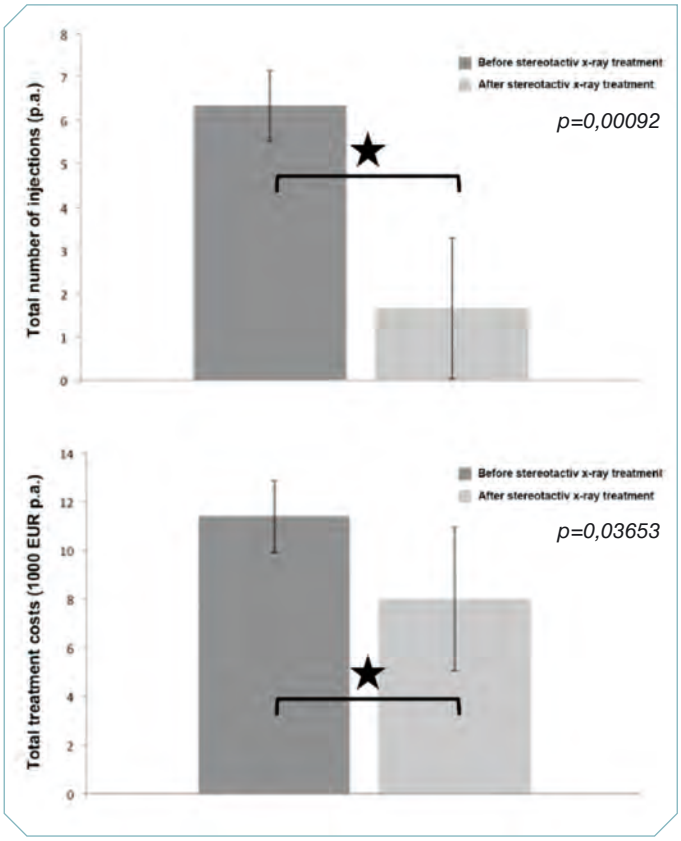
The *INTREPID* study has shown that stereotactic radiation treatment with the Oraya Therapy system has a safety profile which is acceptable and that in select neovascular AMD patients the treatment can reduce the amount of injections patients need.

## CRITERIA DEFINED BY INTREPID STUDY

Statistical analysis of the *INTREPID* study results has defined the population in whom Oraya Therapy will be most effective. They are neovascular AMD patients whose eyes have three principal characteristics, a macular volume of subretinal fluid greater than 7.4mm$^3$, lesions less than 4.0mm in diameter and no significant amount of fibrosis. Previous AMD studies have shown that patients with these characteristics account for 60 per cent of the neovascular AMD population.

Diagnostic techniques for selecting patients should include visual acuity testing, fluorescein angiography, and optical coherence tomography (OCT). Axial length should also be measured for proper dosimetry and to avoid the treatment highly myopic or highly hyperopic. Following Oraya Therapy, patients should be monitored as usual with visual acuity testing and with OCT to detect the presence of subretinal fluid.

Dr Ranjbar and his associates use the same selection criteria for Oraya Therapy as defined by the *INTREPID* study, except that instead of requiring a minimum of three injections within the previous 12 months, they required a minimum of six injections.




*Oraya Therapy reduced injection rate for chronic patients at 12 months*

## SIX AND 12-MONTH RESULTS

In 2014 they treated eight patients with Oraya Therapy, six of whom have been followed closely for a year. In 2015 they treated a further 45 patients, of whom 37 have been followed closely.

Following their radiation therapy, patients continued with their anti-VEGF injections on a PRN basis. They received injections when there was persistent or increased subretinal fluid, an increase in central retinal thickness, the presence of new or increased macular haemorrhage, or a decrease in best corrected visual acuity (BCVA).

He presented the 12-month results of the six patients they treated in 2014 and who had a close follow-up. Their lesion size was less than 4.0mm and the patients' demographics were those typical for AMD patients.

The patients' preoperative BCVA had a mean value of 0.52 and ranged from 0.2 to 0.9, and they received a mean of 6.33 injections in the 12 months prior to undergoing Oraya, with a range from five to seven injections.

At 12 months' follow-up, visual acuity had not changed significantly, with a mean value of 0.5 and a range from 0.1 to 0.9 (p =0.61). Patients required a mean of only 1.67 injections, amounting to a 75 per cent reduction (p= 0.00092).

Moreover, two patients needed no injections at all during the first 12 months after treatment, compared to five and seven injections before treatment. Another patient required only one injection after the radiation treatment, compared to seven injections the previous year.

Furthermore, from an economic point of view, the cost of treatment was significantly lower during the 12 months after Oraya Therapy compared to the 12 months before (p=0.03653).

Among the 37 patients with just six months of follow-up, there was a slight but insignificant increase in visual acuity (p=0.0688) and a trend towards a reduced need for anti-VEGF treatment (p=0.0519). However, there was a significant reduction in central retinal thickness (p=0.0231).

In addition, regarding safety, there was no statistically significant change in the thickness of the nerve fibre layer.

"The real-life results are very encouraging if the criteria for best responders are respected. It is important to inform the patient early regarding risks and benefits of the therapy and set realistic expectations," Dr Ranjbar said.

# The Swiss Experience

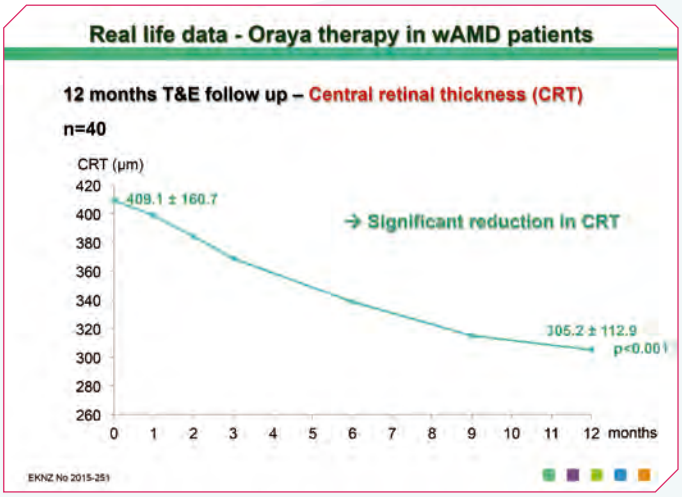
**Katja Hatz MD | khatz@vistaklinik.ch**

Katja Hatz MD, Vista Klinik EyeRAD Swiss Medical Centre in Basel, Switzerland, followed with a presentation detailing the promising one-year results achieved with Oraya Therapy at her centre.

"We reached a significant reduction in central retinal thickness and at 12 months we have a stable visual acuity and a significant increase in the maximum recurrence-free interval and a reduction in OCT morphological choroidal neovascularisation (CNV) activity signs," Dr Hatz said.

She noted that she and her associates have been performing Oraya Therapy treatments since 2013, and so far they have 40 patients with 12 months of follow-up.

The patients fit the usual criteria for Oraya Therapy. That is, they had persistent CNV activity requiring frequent treatments, they had lesions less than 4.0mm in diameter and they had no advanced fibrosis or pigment epithelial dystrophy. In addition, all were able to sit quietly with a slightly bowed head for the 30-minute duration of treatment.




> We reached a significant reduction in central retinal thickness and at 12 months we have a stable visual acuity...

All of the patients had a long history of anti-VEGF treatment on a treat-and-extend basis with a mean duration of 36 or 37 months and a mean of 25.8 anti-VEGF injections. The agents they received were aflibercept in 67.5 per cent of patients and ranibizumab in 32.5 per cent of patients. Their baseline visual acuity was 0.44 and their mean central retinal thickness was 409.1µm (range: 195-883µm).

During the six months prior to undergoing Oraya Therapy, their mean maximum recurrence-free interval was 4.38 months. Most were still receiving anti-VEGF injections at four-week intervals prior to the treatment and a few received the injections at six-week intervals.

## MORPHOLOGICAL IMPROVEMENTS TAKE TIME

Dr Hatz noted that during the first months after Oraya Therapy there was only a small but insignificant change in mean central retinal thickness. However, after about three months the central retinal thickness had decreased to around 365 microns and continued to decease steadily, levelling off at around nine months. At 12 months the mean central retinal thickness was 305.2µm, a decrease of more than 100µm from the baseline value (p<0.001).

Furthermore, during the 12 months after Oraya Therapy the mean maximum recurrence-free interval nearly doubled, increasing to 7.41 weeks, compared to 4.38 weeks during the 12 previous months (p<0.001). That corresponded to a reduction in morphological neovascular activity signs detected by OCT. That is, prior to Oraya Therapy, 90 per cent of patients had subretinal and/or intra-retinal fluid prior

to the treatment, compared to only 35 per cent of patients at a follow-up of one year.

As in Dr Ranjbar's results, there was no significant change in the BCVA over the 12 months.

## MAY BE USEFUL IN CHALLENGING CASES

Dr Hatz noted that among the patients she has treated with Oraya Therapy there have been some difficult cases in which the treatment has been successful.

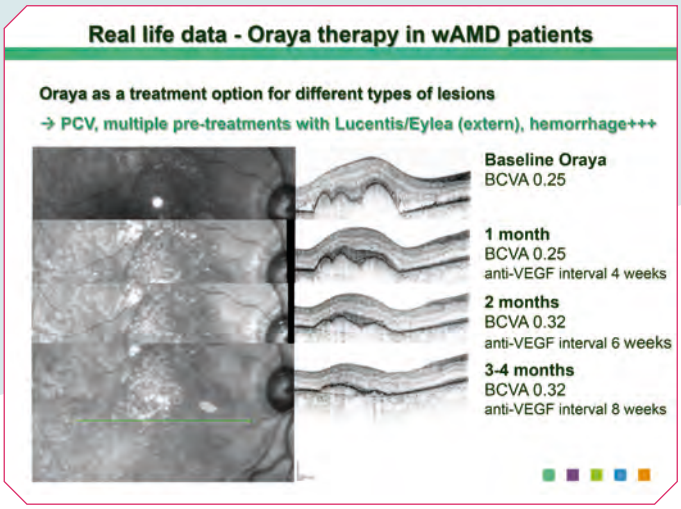
As an example, she described the case of a neovascular AMD patient with polypoidal choroidal vasculopathy (PCV) who had received multiple treatments with Lucentis and Eyelea and was referred to her centre with large haemorrhage and presented with the BCVA of 0.25. At that time he was receiving anti-VEGF treatment every four weeks.

By one month following Oraya Therapy, the pigment epithelial detachment had settled considerably. In addition, it was possible to extend the treatment interval to six weeks, at two months, and to eight weeks at three months.

She also saw improvements in an advanced and highly refractory female patient whose lesion size was slightly larger than 4.0mm. The patient had received over 40 injections, and was receiving the injections at monthly intervals. Therefore, she was very desirous of undergoing Oraya Therapy, a request to which Dr Hatz acceded.

For the first eight months no change was detectable by OCT, but by about nine months the macula was completely dry and has remained so ever since. Moreover, it became possible to extend her treatment intervals.

The Oraya Therapy procedure usually takes between 20 and 30 minutes to perform, including all of the positioning of the patient. She noted that it is generally the practice at her centre




to perform Oraya Therapy in the interval between injections rather than on the same day. That is largely due to logistical reasons and because both procedures are best performed on an undisturbed eye.

She added that the treatment is very well tolerated. All the patients they have treated have been very experienced anti-VEGF patients and they frequently report that Oraya Therapy treatment was easier to undergo than the injections.

"I think that the combination of Oraya Therapy and anti-VEGF injections is a good option for the treatment of neovascular AMD. Always keep in mind that continued anti-VEGF treatment is necessary and try to extend the intervals whatever scheme you are using," she added.

# Oraya Therapy in Treatment-Naïve Patients

**Christopher Brand FRCOphth | christopher.brand@sth.nhs.uk**

The ability of Oraya Therapy to reduce the need for repeated anti-VEGF injections means that it may reduce the chance of visual acuity loss from undertreatment. First-line adjunctive therapy in treatment of naïve neovascular AMD with both anti-VEGF and Oraya Therapy may take best advantage of the combination's synergistic effect and allow better visual recovery with a lower number of injections from starting treatment, said Christopher Brand FRCOphth, Consulting Ophthalmologist, Sheffield Teaching Hospitals, UK.

"My message for today is that Oraya Therapy results in superior visual acuity in an environment of probable under-treatment, while at the same time reducing the injection frequency," he said.

Audits from electronic medical records (EMR) reported in peer-reviewed publications and data from the *LUMINOUS* study, for which he is the UK chief investigator, indicate that the improvement found in pivotal trials cannot be achieved in the real world and that may be a result of under-injection.

He first began using Oraya Therapy in treatment-naïve patients on 21 May 2014, and has performed over 200 treatments to date. He presented the results of the first 25 patients who reached 12 months from the first Lucentis injection, plus the results from the first 58 patients to reach six months after their first injection. Data capture was on every patient who received Oraya Therapy as a result of using electronic patient records.

> ... Oraya Therapy results in superior visual acuity... while at the same time reducing the injection frequency

The patients included were newly diagnosed neovascular AMD whose fundus photographs and fluorescein angiograms showed active neovascular lesions that were occult, minimally classic, predominantly classic or retinal angiomatous proliferation (RAP), but not polypoidal. In addition, all lesions had a greatest linear dimension less than 4.0mm, centred on the fovea and no significant fibrosis.

The treatment protocol involved one initial Lucentis injection and Oraya radiotherapy within the next 14 days of the first injection. They were also mandated to have two more injections during the first three months of treatment and were treated on a PRN basis thereafter.

Using a "historical" control group, Dr Brand selected consecutive patients from a list of 236 new AMD patients who started anti-VEGF treatment on a PRN basis from April 2013 to March 2014. To draw a statistical comparison with the Oraya Therapy group, more than 40 patients were required. Using each patient's code number in his centre's

EMR system, he looked at the fluorescein angiography and OCT image of each patient and made the decision whether he would have offered them Oraya Therapy had they been referred to him. Of the 45 patients who perfectly fit his treatment criteria, four did not reach one year follow-up for various reasons and were excluded.

The active treatment and control groups were similar in age and gender distribution, with around two-thirds in each group being women. Regarding lesion type, approximately 40 per cent of each group had occult lesions, in the comparator group three per cent had minimally classic lesions and four per cent had predominantly classic or classic lesions, compared to 14 per cent in both categories in the Oraya group. In addition, nearly half (47 per cent) in the control group had retinal angiomatous proliferation, compared to 10 per cent in the Oraya group.

## GREATER VISUAL ACUITY IMPROVEMENTS WITH ORAYA THERAPY

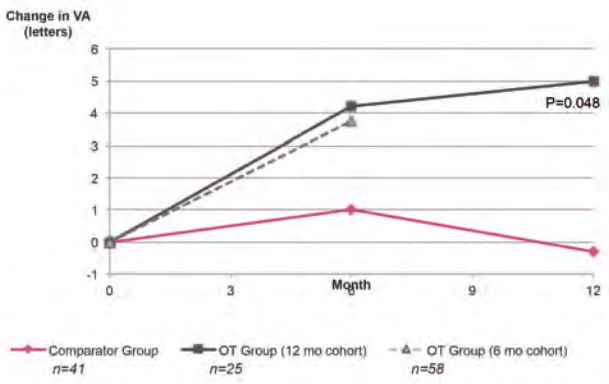
At six months follow-up, patients in the Oraya group had a mean gain of four letters of visual acuity, compared to a gain of only one letter in the control group. Furthermore, by 12 months' follow-up, the patients in the Oraya Therapy group had gained a mean of five letters from baseline visual acuity while the those in the control group had lost a mean of 0.3 letters of visual acuity (p=0.048).

Dr Brand noted that the reason for the seemingly poor results in the comparator group compared to those generally reported with anti-VEGF treatment was likely due to the fact that the patient's neovascular AMD was diagnosed early. In the Oraya and control groups, 40 per cent of patients had a visual acuity of 6/12 or better at baseline. The results in the control group were therefore not that bad. He also pointed out that by six months, 60 per cent in the Oraya group had a visual acuity of 6/12 or better, and that improvement was maintained among those reaching 12 months of follow-up, again a statistically significant result.

Furthermore, in the Oraya Therapy groups there was a loss of 15 or more letters in 3.4 per cent of eyes at six months and in four per cent of eyes at 12 months. That compared to a loss of 15 or more letters in 14.6 per cent of eyes in the control group at 12 months. Similarly, in the Oraya group there was a gain of 15 or more letters in 17.2 per cent of eyes at six months and 16 per cent of eyes at 12 months, compared to only 9.8 per cent of eyes in the comparator group at 12 months.

Regarding injection frequency, 60 per cent of those in the Oraya group required one or no anti-VEGF injections during the nine months following the three-month loading dose period, compared to 34 per cent in the control group.

### Vision results

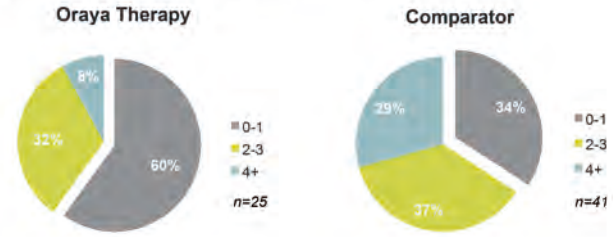



### Injections at 12 months after diagnosis

| Oraya Therapy | Comparator |
|---|---|
| 4.60 | 5.63 |

Includes 3 loading injections

**Comparison of number of injections *after* loading**




Furthermore, eight per cent in the Oraya Therapy group needed four or more anti-VEGF injections following the loading phase, compared to 29 per cent in the control group.

At 12 months, the patients in the Oraya group had required an average total of 4.60 injections, whereas the comparator group required an average total of 5.63 injections. These results compare favourably with those from the UK EMR one-year data reported in peer-reviewed publications, which show an improvement of two letters with 5.8 injections.

> Oraya Therapy was well tolerated by patients, and 60% in the Oraya group required 0 or 1 injection in the 9 months after loading

The results are also equivalent to those achieved in some of the more rigorously controlled clinical trials with anti-VEGF agents. For example, in the *IVAN* study, patients gained 5.5 letters of visual acuity after seven injections.

Regarding safety, Dr Brand noted that he and his associates found no evidence of microvascular changes in any eye, including one eye that underwent repeat fluorescein angiogram when presenting with neovasular AMD in the other eye. He cautioned, however, that the development of microvascular changes usually occurs 24-36 months after Oraya Therapy.

Dr Brand noted that two patients in the six-month Oraya result group had not received the mandated three anti-VEGF injections, one patient one injection and the other two. Neither patient had required a further injection at the six-month review. He therefore suggested that a treat-and-extend scheme might be a viable option from the very start of the combination treatment.

He added that his future work will include looking at OCT for anatomical correlates of visual improvement, analysing the data for the 12-month period after the loading dose and continuing to track safety and efficacy. He stressed that, without auditing our results, it can be difficult to tell how successful or unsuccessful a treatment is.

"In summary, Oraya Therapy was well tolerated by patients, and compared to standard anti-VEGF monotherapy controls in Sheffield, it offers superior visual outcomes and fewer injections. One third of patients did not need more injections at 12 months review following three mandated injections, and at six months, 60 per cent did not require more injections," said Dr Brand.

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Sponsored by an educational grant
from Oraya Therapeutics, Inc.

In the USA, the IRay® Radiotherapy System is an investigational device and is not available for sale.

Further information about Oraya Therapy and Oraya Therapeutics, Inc. can be found at www.orayainc.com

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Dec 2015/Jan 2016