IRay® for wet age-related macular degeneration

November 2013
Technology, Company and Licensing

Register ID WP171
Technology name The IRay® Radiotherapy System
Patient indication For patients with wet age-related macular degeneration

Description of the technology

The IRay® Radiotherapy System is a non-surgical treatment for wet age-related macular degeneration (AMD) that delivers low-energy X-rays to the back of the eye with the aim of slowing disease progression by reducing vascular growth, inflammation and scarring. The system consists of an X-ray tube, a patient interface, an eye-stabilising device which couples the patient’s eye to the X-ray system (I-Guide™), an eye tracking system, a graphical user interface and treatment planning software.

The IRay® device is designed for use in a typical medical office, and the treatment can be administered in a clinic or ambulatory setting. The patient is seated at the device interface and the I-Guide™ system is attached to the eye via a contact lens. The eye is then tracked using infrared cameras. The X-ray tube delivers three low-energy X-ray beams through the eye which overlap on the macula. If the patient’s eye moves more than an acceptable amount in the x-, y-, z- or rotational axis, the device immediately shuts down. Ninety per cent of the beam is centred on a 4 mm area of the macula. Consequently, the low-energy radiation does not pose any risk to the lens, optic nerve or brain. Clinical trials have reported a radiation time of approximately 15 minutes.

The IRay® Radiotherapy System has many advantages over current stereotactic radiation treatments for wet AMD. For example, it does not require surgery, the dose of radiation administered is not user dependent, and the real-time tracking of eye movement enables accurate radiation delivery.

Company or developer

The IRay® Radiotherapy System is manufactured by Oraya Therapeutics, Inc. (Newark, CA, United States of America).

Reason for assessment

The IRay® Radiotherapy System is a novel, non-invasive treatment for wet AMD. Current treatments are invasive, require repeat application, produce variable results and are expensive.
Stage of development in Australia

- Yet to emerge
- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

Licensing, reimbursement and other approval

At present, the IRay® Radiotherapy System is not listed on the Australian Register of Therapeutic Goods and has not received a premarket approval or premarket notification 510(k) from the United States Food and Drug Administration. However, the system has received a European CE mark.7

Australian Therapeutic Goods Administration approval

- Yes
- No
- Not applicable

Technology type

Device

Technology use

Therapeutic

Patient Indication and Setting

Disease description and associated mortality and morbidity

AMD is a progressive disease resulting from the gradual deterioration of the central retina (macula). The macula is a specialised region of the retina that is dense in photoreceptor cells (cone cells). These cells are responsible for colour vision and visual acuity in bright conditions.8 AMD is characterised by the gradual loss of these photoreceptors, resulting in eventual blindness. However, only central vision is affected; peripheral vision remains relatively unchanged. Currently, the pathogenesis of AMD is unknown.9

AMD is initially asymptomatic and may go unnoticed for some time. Symptoms typically appear in older adults (>50 years) and progress gradually or rapidly reflecting dry and wet AMD respectively. Common symptoms include blurred or blind spot in the centre of the field of vision; hallucinations of geometric shapes, animals or people; and a decrease in the intensity or brightness of colours. The symptoms of AMD significantly reduce quality of life as many patients report difficulty reading, recognising faces and driving.10 In addition, both dry and wet AMD often lead to additional eye problems. For example, wet AMD significantly
increases the likelihood of some types of retinal detachments resulting in permanent blindness through the formation of a scar.

AMD is divided into early and late disease stages. Early AMD is associated with the accumulation of intra- and extracellular proteins, lipids and cellular components (drusen) and the infiltration of microglia or macrophages underneath the retinal epithelium. Although these events do not affect vision, they are precursors to late AMD. It is worth noting that not all patients with early AMD will progress to the late stage.  

Late AMD is divided into two categories: dry (non-exudative or atrophic) or wet (exudative or neovascular). Wet AMD is characterised by the abnormal growth of blood vessels (neovascularisation) beneath the retina. These blood vessels invade and break through the retina, protruding into the macula. The vessels leak blood and fluid and allow macrophages to infiltrate the macula. Both events lead to photoreceptor degradation. Current therapies aim to reduce inflammation and inhibit blood vessel growth.

The rate of progression from early to late AMD is difficult to determine and may occur rapidly or slowly among individuals. However, the Age Related Eye Disease Study (AREDS) determined approximately 20 per cent of participants with early AMD progressed to late AMD after five years—corresponding to approximately four per cent each year. Similar results have been obtained within Australia. The Blue Mountain eye study determined the risk of progression to late stage of AMD was 3.7 per cent per year in a sample of 3,582 Australians. In addition, women were more likely to progress to late AMD compared to men (4.4% and 2.8% respectively).

In terms of vision loss, however, the progression from moderate to severe appears to occur less rapidly than the progression from mild to moderate. There are numerous risk factors associated with the development of AMD. However, age and family history of AMD are the greatest risk factors. In addition, lifestyle factors such as smoking, obesity and hypertension are also associated with the development of AMD.

**Number of patients**

In 2010, approximately 1.023 million Australians had AMD in at least one eye, of which approximately 856,000 and 167,000 was attributable to early and late AMD respectively. Further analysis of late AMD determined a higher prevalence of the wet form compared to the dry (112,000 and 55,000 respectively). In the absence of effective preventative or treatment measures, these figures are anticipated to increase due to the ageing demographic. By 2030, it is estimated that 1.77 million Australians will be diagnosed with AMD in at least one eye, representing an increase of 70 per cent.

AMD is more prevalent in women (2.92 per 100,000) than in men (1.97 per 100,000), and its incidence is strongly correlated with increasing age. For example, the prevalence rate for
bilateral AMD is 5.14 per cent in people aged 80 to 84, compared with 26.67 per cent in people aged 90 and above. In addition, the prevalence of bilateral AMD in people aged 90 and above is anticipated to double from 35,521 in 2010 to 78,774 by 2030. It is worth noting that two thirds of all adults older than 80 years show some signs of early AMD.

AMD is the second most common cause of visual impairment and the leading cause of blindness in Australia. In 2010, 107,000 Australians were visually impaired due to late AMD. Of these, 29,913 were estimated to have mild visual loss, 21,180 to have moderate visual loss and 56,098 to have severe visual loss. In addition, 61,000 Australians were legally blind due to late AMD, of which wet AMD was the more likely cause of blindness than dry AMD (52,000 and 9,000 respectively).

Speciality Ophthalmology
Technology setting Ambulatory Care, General or Specialist Hospital

Impact

Complementary technology

The IRay® Radiotherapy System is designed to be used in conjunction with current pharmacological therapies for wet AMD.

Current technology

At present, there is no cure for wet AMD. Current treatments aim to stop the worsening of vision by slowing the growth of blood vessels beneath the retina. Pharmacological therapies inhibit vascular endothelial growth factor (VEGF), a key signalling protein which promotes the growth of blood vessels. Anti-VEGF therapies include monoclonal antibodies such as ranibizumab (Lucentis®) and bevacizumab (Avastin®), which are injected into the eye (intravitreal). Following these injections patients are monitored monthly and additional maintenance injections may be required. Both therapies are manufactured by Genentech, Inc. (San Francisco, CA, United States of America) and are listed on the Pharmaceutical Benefits Scheme (PBS) in Australia (Table 1). Common side effects include: dry or itchy eyes, headache, nausea, reddening of the eye, eye pain, sensitivity to light, bleeding in or around the eye, decrease or changes in vision and seeing floaters or small specks.

The VIDION® ANV® Therapy System (NeoVista® Inc., Fremont, CA, United States of America) is another novel radiotherapy device designed for the treatment of wet AMD.
Table 1  Medicare and pharmaceutical benefit schedule items relating to wet AMD

<table>
<thead>
<tr>
<th>Item number (MBS)</th>
<th>Descriptor</th>
<th>Fee</th>
</tr>
</thead>
</table>
| 42739            | Paracentesis of anterior chamber or vitreous cavity, or both, for the injection of therapeutic substances, or the removal of aqueous or vitreous humours for diagnostic or therapeutic purposes, 1 or more of, as an independent procedure, for a patient requiring anaesthetic services. (Anaes.) | Fee: $300.75  
Benefit 75%: $225.60  
Benefit 85%: $255.65 |

<table>
<thead>
<tr>
<th>Code/prescriber (PBS)</th>
<th>Descriptor</th>
<th>Fee</th>
</tr>
</thead>
</table>
| 1382R/Medical Practitioner | Ranibizumab (Lucentis®) 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial | Dispense price for maximum quantity: $1431.37  
Max price to consumer: $36.10 |
| 2168D/Medical Practitioner | Aflibercept (Evlea®) 4 mg/0.1 mL injection, 1 x 0.1 mL vial | Dispense price for maximum quantity: $1431.37  
Max price to consumer: $36.10 |
| 4400N/Medical Practitioner (Public Hospital) | BEVACIZUMAB Injection  
Avastin® (bevacizumab 100 mg/4 mL injection, 1 x 4 mL vial)  
Avastin® (bevacizumab 400 mg/16 mL injection, 1 x 16 mL vial) | Dispense price for maximum quantity: $3971.33  
Max price to consumer: $36.10 |
| 7243F/Medical Practitioner (Private Hospital) | BEVACIZUMAB Injection  
Avastin® (bevacizumab 100 mg/4 mL injection, 1 x 4 mL vial)  
Avastin® (bevacizumab 400 mg/16 mL injection, 1 x 16 mL vial) | Dispense price for maximum quantity: $4062.10  
Max price to consumer: $36.10 |

Avastin® for the treatment of wet AMD is used off-label, its primary use is to treat colorectal cancer.  
MBS=Medicare benefits scheme; PBS=Pharmaceutical benefits scheme

**Diffusion of technology in Australia**

The diffusion of the IRay® Radiotherapy System within Australia could not be determined through review of published literature.

**International utilisation**

The IRay® Radiotherapy System has completed clinical trials in five European countries, although the largest body of evidence originates from Mexico (5 published trials) (Table 2).


<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Czech Republic</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

**Cost infrastructure and economic consequences**

Capital costs associated with the IRay include the purchase of the radiotherapy system. The IRay® Radiotherapy System is designed to be installed in a typical medical office and can be operated by an ophthalmologist without additional facility, staff or patient shielding requirements. The main additional costs associated with the IRay include the single-use contact lens, staff training and certification and registration of irradiating equipment.\(^{16}\)

The first clinical centre (United Kingdom) to offer the IRay therapy for wet AMD reported a treatment cost of GB£3,995 (approximately A$5,262) per eye in 2012.\(^{17}\)

**Ethical, cultural or religious considerations**

No ethical, cultural or religious considerations were identified in the published literature.

**Evidence and Policy**

**Safety and effectiveness**

One randomised controlled trial (RCT) (level II Intervention evidence) and three case series (level IV Intervention evidence) evaluating the IRay in patients diagnosed with wet AMD were included in the technology brief. The RCT compared the IRay® Radiotherapy System administered at 16 Gy or 24 Gy to sham therapy. The three case series studies prospectively analysed the IRay® Radiotherapy System; two evaluated a 16 Gy dose of radiation and one evaluated a 24 Gy dose. The safety and efficacy of the IRay® Radiotherapy System was assessed in a total of 280 patients. The outcomes reported across all four studies included visual acuity (acuteness or clearness of vision), the number of ranibizumab injections required and changes in central subfield thickness, and the greatest linear diameter of the choroidal neovascular (CNV) lesion as measured by optical coherence tomography (indications of AMD progression—a positive or negative score indicating an increase or a decrease in sub-retinal fluid, respectively). A summary of the included studies is outlined in Table 3.
Table 3  Characteristics of included studies on patients with wet AMD

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td>II</td>
<td>IV (prospective)</td>
<td>IV (prospective)</td>
<td>IV (prospective)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>IRay (16 Gy) = 75</td>
<td>28</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Interventions</td>
<td>IRay (24 Gy) = 75</td>
<td>Sham = 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>12 months</td>
<td>6 and 12 months</td>
<td>6 and 12 months</td>
<td>6 and 12 months</td>
</tr>
<tr>
<td>Conflict of interest</td>
<td></td>
<td>The first author and three other authors are consultants for Oraya Therapeutics, Inc. One author is an equity owner and consultant for Oraya Therapeutics, Inc. One author is an employee of Oraya Therapeutics, Inc. One author is a consultant and equity owner in Oraya Therapeutics, Inc.</td>
<td>The first author and three other authors are consultants for Oraya Therapeutics, Inc. One author is an equity owner and consultant for Oraya Therapeutics, Inc.</td>
<td>The study was funded by Oraya Therapeutics, Inc. Four authors are consultants for Oraya Therapeutics, Inc. One author is a consultant and equity owner in Oraya Therapeutics, Inc.</td>
</tr>
</tbody>
</table>

The first author and three other authors are consultants for Oraya Therapeutics, Inc. One author is an equity owner and consultant for Oraya Therapeutics, Inc. One author is an employee of Oraya Therapeutics, Inc.

One author is a consultant and equity owner in Oraya Therapeutics, Inc.
Jackson et al. 2013

An RCT (level II Intervention evidence) was conducted across 21 centres in Europe by Jackson et al. Between December 2009 and April 2011, 230 patients were included who had a choroidal neovascularisation (CNV) resulting from wet AMD, at least three intravitreal ranibizumab or bevacizumab injections within the previous year, a CNV lesion smaller than 12 disc areas with the greatest linear dimension less than 6 mm, and a best-corrected visual acuity (BCVA) of 25 to 75 letters in the study eye and at least 20 letters in the remaining eye. In addition, patients were required to be at least 50 years of age and women were required to be surgically sterilised, one year post-menopause or not planning to become pregnant during the study.

Upon inclusion, patients received an intravitreal injection of ranibizumab (day 0). Between days 1 and 14, patients were randomly assigned (using a dynamic randomisation algorithm) in a 2:1:2:1 ratio to one of four treatment arms: IRay (16 Gy dose of radiation), sham IRay (16 Gy), IRay (24 Gy) or sham IRay (24 Gy). Patients received a single treatment with the IRay® Radiotherapy System and no additional treatments were performed. Additional ranibizumab injections were administered if patients demonstrated an increase of 100 µm in central subfield thickness, new or increased macular haemorrhage or a loss in BCVA of five or more letters since their last visit or baseline reading. The two sham arms were pooled for analysis. Patients were assessed every four weeks for 52 weeks. All the patients and study personnel were masked to treatment allocation. There were no losses to follow-up. Baseline patient demographics did not differ between the groups ($p>0.05$ for all variables) (Table 4).

**Table 4** Baseline patient characteristics

<table>
<thead>
<tr>
<th>Baseline patient characteristic</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRay 16 Gy (n=75)</td>
</tr>
<tr>
<td>Mean (±SD) age (years)</td>
<td>73.4 (7.2)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>75 (100)</td>
</tr>
<tr>
<td>Right eye, n (%)</td>
<td>39 (52)</td>
</tr>
<tr>
<td>Mean (±SD) duration of wet AMD</td>
<td>12.8 (7.3)</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) number of prior anti-</td>
<td>5.0 (3.9)</td>
</tr>
<tr>
<td>VEGF injections</td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) time since last</td>
<td>3.7 (2.9)</td>
</tr>
<tr>
<td>injection (months)</td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) baseline visual acuity (number of ETDRS letters)</td>
<td>57.9 (12.7)</td>
</tr>
</tbody>
</table>

SD=standard deviation; VEGF=vascular endothelial growth factors; ETDRS=early treatment diabetic retinopathy study
Safety

No deaths were reported. The number and severity of adverse events did not differ between the three treatment groups. Adverse events were reported in 55, 67 and 62 per cent of patients in the 16 Gy, 24 Gy and sham groups respectively. The percentage of adverse events attributable to the IRay® Radiotherapy System was 19, 26 and 10 per cent in the 16 Gy, 24 Gy and the sham group, respectively. Serious adverse events were noted in 15, 8 and 8 per cent of patients in the 16 Gy, 24 Gy and sham groups respectively. The types of adverse events were not reported.

Efficacy

The number of ranibizumab injections administered differed significantly between the three treatment groups. Patients treated with either IRay 16 Gy (p=0.0013) or 24 Gy (p=0.004) required fewer injections over 52 weeks compared with the sham group (Table 5). In addition, more of the patients treated with either the IRay 16 Gy or 24 Gy did not require any additional ranibizumab injections compared with the sham group (p=0.02). The reasons for administering ranibizumab injections, however, did not differ between the treatment groups.

Table 5  Characteristics of ranibizumab treatments at 52 weeks post IRay treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD) number of ranibizumab injections</td>
<td></td>
</tr>
<tr>
<td>2.6 (2.5)</td>
<td>2.4 (2.4)</td>
</tr>
<tr>
<td>Number of patients not requiring additional</td>
<td></td>
</tr>
<tr>
<td>injections (%)</td>
<td>17 (23%)</td>
</tr>
<tr>
<td>Indication for ranibizumab, %*</td>
<td></td>
</tr>
<tr>
<td>&gt;100µm increase in central subfield thickness</td>
<td>50</td>
</tr>
<tr>
<td>Loss of &gt;5 ETDRS letters</td>
<td>52</td>
</tr>
<tr>
<td>New or increased macular haemorrhage</td>
<td>9</td>
</tr>
</tbody>
</table>

*Some patients had more than one indication

ETDRS=early treatment diabetic retinopathy study letters, SD=standard deviation

Overall, the mean change in visual acuity was minimal across all treatment groups (Table 6). In all groups, approximately 90 per cent of participants lost fewer than 15 letters, 55 per cent had no change or gained some letters, and four per cent gained at least 15 letters over one year.
Table 6  
Change in visual acuity at 52 weeks post IRay treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IRay 16Gy (n=75)</th>
<th>IRay 24 Gy (n=75)</th>
<th>Sham (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) change in ETDRS letters</td>
<td>-0.28 (8.77)</td>
<td>+0.40 (10.33)</td>
<td>-1.57 (11.90)</td>
</tr>
<tr>
<td>Lost &lt;15 letters</td>
<td>93%</td>
<td>89%</td>
<td>91%</td>
</tr>
<tr>
<td>Gained ≥ 0 letters</td>
<td>53%</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td>Gained ≥ 15 letters</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

SD= standard deviation; ETDRS=early treatment diabetic retinopathy study letters

The mean central subfield thickness and greatest linear diameter of the CNV lesion had decreased in all treatment groups at 52 weeks (Table 7). The IRay 16 Gy and IRay 24 Gy produced the largest change in mean central subfield thickness, followed by the sham group. In contrast, however, the sham group reported the greatest mean decrease in linear diameter of the CNV lesion. However, the statistical significance of these differences was not reported.

Table 7  
Mean change in CNV lesion size at 52 weeks post IRay treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IRay 16Gy (n=75)</th>
<th>IRay 24 Gy (n=75)</th>
<th>Sham (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) change in central subfield thickness (µm)</td>
<td>-85.90 (11.51)</td>
<td>-70.39 (12.47)</td>
<td>-33.51 (12.65)</td>
</tr>
<tr>
<td>Mean (±SE) change in greatest linear diameter of CNV lesion (mm²)</td>
<td>-0.10 (0.04)</td>
<td>-0.16 (0.06)</td>
<td>-0.18 (0.06)</td>
</tr>
</tbody>
</table>

SD= standard deviation; SE= standard error; CNV=choroidal neovascularisation

Morales-Canton et al. 2011

A case series (level IV Intervention evidence) was conducted at a single institution in Mexico by Morales-Canton et al.5 Twenty-eight participants with wet AMD were enrolled who had evidence of subfoveal choroidal neovascularisation and who were at least 50 years of age; women were required to be one year post-menopause or surgically sterilised. Patients were excluded if they had previous surgical treatment for AMD (submacular surgery, thermal laser photocoagulation, photodynamic therapy and transpupillary thermotherapy), diabetes mellitus or elevated fasting blood glucose.

Patients received two mandatory injections of ranibizumab on days 0 and 30. Between days 1 and 14, patients received a single treatment with the IRay system (16 Gy). Additional ranibizumab injections were offered to patients who demonstrated a loss of 10 or more early treatment diabetic retinopathy study (ETDRS) letters, an increase of 100 µm in central
foveal thickness, development of a new subretinal haemorrhage or new choroidal neovascularisation. Patients were assessed monthly and safety and efficacy data were published separately for 6-5 and 12-month18 follow-up.

Two patients were subsequently excluded from the 6-month efficacy data and three from the 12-month follow-up. One patient was initially misdiagnosed with choroidal neovascularisation, another missed the 6- and 12-month follow-up visits and one patient died between 10 and 11 months.

Patient characteristics were not reported.

Safety

No deaths occurred as a result of the IRay device. No serious adverse events were reported. Asymptomatic superficial punctate keratopathy, a minor adverse event, was experienced by all patients. Thirty-three additional adverse events were reported which included: conjunctivitis (n=2), eyelid inflammation (n=4), vitreous floaters (n=1), conjunctival haemorrhage (n=3), decreased vision (n=3), eye pain (n=3), increased tear secretion (n=1), eye strain (n=2), cataract (n=2), increased blood within the eye (ocular hyperemia) (n=1), eyelashes growing inwards towards the eye (trichiasis) (n=1), blurred vision (n=2), foreign body sensation (n=1), viral conjunctivitis (n=3), herpes zoster infection (n=1), external stye (hordeolum) (n=1) and increased intraocular pressure (n=2).

Efficacy

A total of 13 and 26 ranibizumab injections were required by the entire patient cohort at the 6- and 12-month follow-up, respectively. This corresponded to a mean (±SD) of 1±1.2 ranibizumab injections per person by 12 months. Fourteen of the 26 patients, however, did not receive any additional injections.

Visual acuity increased over 12 months. The mean (±SD) ETDRS scores increased from 46.6 (21.5) at baseline to 55.6 (19.3) letters at six months and 55.8 (20.5) at 12 months. At six months, 81 per cent of (n=21/26) patients reported no change or a gain of some letters. By 12 months, however, this number decreased to 76 per cent (n=19/25). In contrast, the number of patients who lost fewer than 15 letters remained similar from 6 to 12 months (96%, n=25/26, and 100%, n=25/25, respectively). At six months, 50 per cent (n=13/26) of patients gained at least 15 letters. However, this percentage decreased slightly (48%) at 12 months (n=12/25).

A subgroup analysis comparing the results of patients who had received previous anti-VEGF injections (previously treated) with those who hadn’t (treatment naïve) found that visual acuity scores were similar between the two groups at the 6- and 12-month follow-up.
Table 8  Change in visual acuity

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall 6-month FU (n=26)</th>
<th>Overall 12-month FU (n=25)</th>
<th>Previous anti-VEGF injections 6-month FU (n=26)</th>
<th>Previous anti-VEGF injections 12-month FU (n=25)</th>
<th>No previous anti-VEGF injections 6-month FU (n=26)</th>
<th>No previous anti-VEGF injections 12-month FU (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost fewer than 15 letters (%)</td>
<td>81</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Gained 0 or more letters (%)</td>
<td>95</td>
<td>76</td>
<td>81</td>
<td>75</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>Gained 15 or more letters (%)</td>
<td>50</td>
<td>48</td>
<td>44</td>
<td>44</td>
<td>60</td>
<td>56</td>
</tr>
</tbody>
</table>

FU = follow up

Changes in central retinal thickness and CNV lesion size were reported every three months up to 12 months (Table 9). Patients treated with IRay (16 Gy) reported a sustained decrease in central retinal thickness, with the maximal decrease observed at six months. Similarly, the greatest linear dimension of the CNV lesion decreased over the 12-month period compared to baseline, with the maximal decrease being observed after nine months.

Table 9  Change CNV lesion size

<table>
<thead>
<tr>
<th>Length of follow-up</th>
<th>Change in central subfield thickness from baseline: mean (range) µm</th>
<th>Mean (±SD) change in the greatest linear dimension of the CNV lesion, mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td></td>
<td>-0.3 (1.2)</td>
</tr>
<tr>
<td>3 months</td>
<td>-0.93 (-487 to +40)</td>
<td>-0.7 (2.2)</td>
</tr>
<tr>
<td>6 months</td>
<td>-1.131 (-720 to +89)</td>
<td>-1.0 (2.5)</td>
</tr>
<tr>
<td>9 months</td>
<td>-0.94 (-583 to +113)</td>
<td>-1.3 (2.4)</td>
</tr>
<tr>
<td>12 months</td>
<td>-1.107 (-609 to +197)</td>
<td>-1.3 (2.4)</td>
</tr>
</tbody>
</table>

Morales-Canton et al. 2012¹⁹

A prospective case series (level IV Intervention evidence) was conducted at a single institution in Mexico by Morales-Canton et al.¹⁹ Nineteen participants were enrolled following a diagnosis of wet AMD. Inclusion and exclusion criteria were identical to those previously outlined by Morales-Canton et al. in 2011.⁵

Patients were treated in the same manner to Morales-Canton et al. 2011⁵, however, the IRay® Radiotherapy System delivered a 24 Gy dose of radiation instead of 16 Gy. Patients were assessed monthly with 6-¹⁹ and 12-month¹⁸ safety and efficacy data available for all 19 patients. Patient characteristics were not reported.

Safety

No serious adverse events were reported. Asymptomatic superficial punctate keratopathy was observed in 53 per cent (n=10) of patients. An additional 17 adverse events were reported which included: conjunctivitis (n=4), inflammation of the eyelid (blepharitis, n=2),
vitreous floaters (n=3), decreased vision (n=1), eye pain (n=1), perceived flashes of light (photopsia, n=1), increased blood within the eye (ocular hyperaemia, n=1), eyelashes growing inwards towards the eye (trichiasis, n=1), allergic conjunctivitis (n=1), eye irritation (n=1) and itchy eye (pruritus, n=1).

**Efficacy**

An additional 19 ranibizumab injections in eight patients were performed over the 12-month period. Eleven patients did not require any additional injections.

Visual acuity improved over the 12-month period. The mean ETDRS (±SD) score increased from 38.3 ± 19.5 at baseline to 46.1 ± 12 by 12 months, representing a mean change of 7.8 ± 12 letters. In addition, of the 19 patients, none lost more than 15 letters, 15 (79%) had no change or gained some letters, five of whom (26%) gained 15 or more letters.

Overall, patients exhibited a decrease in both central retinal thickness and greatest linear dimension of the CNV lesion (Table 10). However, in contrast to the central retinal thickness, which decreased over the 12-month period, the greatest linear dimension of the CNV lesion increased during the first three months after treatment. However, the CNV lesion decreased over the next nine months.

**Table 10**  
Change in CNV lesion size

<table>
<thead>
<tr>
<th>Length of follow-up</th>
<th>Change in Central retinal thickness from baseline: mean (range) µm</th>
<th>Mean (±SD) change in the greatest linear dimension of the CNV lesion mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>-</td>
<td>+0.1 (0.7) (n=15)</td>
</tr>
<tr>
<td>3 month</td>
<td>-31 (-427 to +272)</td>
<td>+0.1 (0.7) (n=16)</td>
</tr>
<tr>
<td>6 month</td>
<td>-50 (-441 to +265)</td>
<td>-1.0 (2.0) (n=17)</td>
</tr>
<tr>
<td>9 month</td>
<td>-86 (-443 to +215)</td>
<td>-1.3 (1.9) (n=11)</td>
</tr>
<tr>
<td>12 month</td>
<td>-87 (-433 to +104)</td>
<td>-0.2 (3.70 (n=9)</td>
</tr>
</tbody>
</table>

**Moshfeghi et al. 2011**³

A prospective case series (level IV Intervention evidence) was conducted at a single centre in Mexico by Moshfeghi et al. Thirteen patients were enrolled in the study following a diagnosis of subfoveal CNV secondary to wet AMD. Patients were excluded from the study if they had received previous treatment for AMD, had a history of diabetes mellitus or had elevated fasting blood glucose. The patients received IRay treatment (16 Gy) delivered to the macula for 15 minutes. Follow-up appointments were scheduled at one week, one month, five weeks and monthly thereafter. At present, the 6-³ and 12-month²⁰ follow-up data are available. Ranibizumab was available to patients as a rescue therapy if they reported a loss of 10 or more ETDRS letters, an increased central foveal thickness (>100µm) or new subretinal haemorrhage. The minimum time between ranibizumab injections was four weeks.
The included patients had a mean age of 72.7 ± 7 years and 62 per cent were women. All patients were of Hispanic descent. The mean ETDRS score at enrolment was 45.5 letters, with 62 per cent of participants reporting a visual acuity of less than 55 letters. One patient received intravitreal bevacizumab injections two months prior to the study start date and was considered a protocol deviation. All 13 patients completed the 6- and 12-month follow-up visits. However, only 12 patients completed the central retinal thickness and the CNV linear dimension measurements at 12 months.

**Safety**

No deaths or serious adverse events were reported. Asymptomatic superficial punctate keratopathy was observed in 10 of the 13 patients immediately following the procedure and was attributed to the IRay device.

**Efficacy**

Over the 12-month period, 12 patients received 31 ranibizumab injections. The mean time until the first injection was 3.9 months. One patient did not receive any injections.

At the 6- and 12-month follow-up, visual acuity remained at levels similar to baseline recordings (44.2 ± 19.2 and 45.2 ± 17.6 ETDRS letters, respectively). No patient gained more than 15 letters at either the 6- or 12-month follow-up. Fifty-four per cent (n=7/13) of patients reported no change or a gain of some letters, while 92 per cent (n=12/13) lost fewer than 15 letters at the 6-month follow-up. These figures were unchanged at the 12-month follow-up.

Central subfield thickness decreased by 127 µm and 117 µm at six and 12 months after treatment, respectively. Similarly, the greatest linear dimension of the CNV lesion decreased by the 6- and 12-month follow-up (0.9±1.2 and 2.1±2.4 mm², respectively).

**Economic evaluation**

No cost effectiveness studies of IRay were identified in the literature.

**Ongoing research**

Current clinical trials are investigating novel methods to inhibit blood vessel growth, reduce inflammation and replace lost photoreceptors in patients with wet AMD. Four clinical trials that are currently underway were identified from searches of the ClinicalTrials.gov website and the Australian and New Zealand Clinical Trials Register (Table 11). All studies are collaborating with or receiving sponsorship from Oraya Therapeutics, Inc.
Table 11  
Current clinical trials evaluating IRay® Radiotherapy System

<table>
<thead>
<tr>
<th>Trial Identifier/ Location</th>
<th>Trial status</th>
<th>N</th>
<th>Details</th>
<th>Diagnosis</th>
<th>Interventions</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01217762/ Mexico</td>
<td>Active but not recruiting</td>
<td>62</td>
<td>Non-randomised comparative study Single centre</td>
<td>VECN secondary to AMD</td>
<td>Patients will receive either: 1. 11 Gy IRay treatment + ranibizumab at 1 month and as required 2. 16 Gy IRay treatment + ranibizumab at 1 month and as required 3. 16 Gy IRay treatment and ranibizumab as required 4. 24 Gy IRay treatment + ranibizumab at 1 month and as required</td>
<td>October 2014</td>
</tr>
<tr>
<td>NCT01521065/ United Kingdom</td>
<td>Recruiting</td>
<td>500</td>
<td>Case series Single centre</td>
<td>CNV secondary to AMD</td>
<td>Patients will receive 16 Gy IRay treatment and ranibizumab</td>
<td>October 2016</td>
</tr>
<tr>
<td>NCT01516294/ Italy</td>
<td>Active but not recruiting</td>
<td>12</td>
<td>Case series Single centre</td>
<td>PCV secondary to AMD</td>
<td>Patients will receive 16 Gy IRay treatment with ranibizumab</td>
<td>March 2014</td>
</tr>
<tr>
<td>NCT01521819/ Italy</td>
<td>Active but not recruiting</td>
<td>12</td>
<td>Case series Single centre</td>
<td>VPED secondary to AMD</td>
<td>Patients will receive 16 Gy IRay treatment with ranibizumab</td>
<td>August 2014</td>
</tr>
</tbody>
</table>

GY= Gray; CNV= Choroidal Neovascularisation; PCV= Polypoidal Choroidal Vasculopathy; VPED= Vascularized Pigment Epithelial Detachment, VECN= Vascularized Exudative Choroidal Neovascularization

**NCT01217762** – The study’s primary outcome is to determine the incidence of radiation-related adverse events. Secondary outcomes include the incidence of ocular adverse events, changes in visual acuity, the mean time to anti-VEGF injection, the number of ranibizumab injections required and changes in total CNV lesion size.

**NCT01521065** – The study’s primary outcome is to determine the number of anti-VEGF injections required during the first 12 months following IRay treatment. Secondary outcomes include time to the first anti-VEGF injection, change in mean BVCA in the treated eye at 12 months and the difference in the visual functioning questionnaire.

**NCT01516294** – The study’s primary outcome is to determine the CNV lesion change as measured by fluorescein angiography at 12 months. Secondary outcomes include the number of ranibizumab injections and changes in visual acuity and polyps over 12 months.

**NCT01521819** – The study’s primary outcome is to determine the CNV lesion change as measured by fluorescein angiography at 12 months. Secondary outcomes include changes in visual acuity.
Other issues

The main benefit of ranibizumab injection is reported to occur in the first three months of treatment, with minimal improvement occurring thereafter. Monthly injections are required to sustain the improvement.

The frequency of anti-VEGF injections in the RCT was lower than is commonly used in clinical practice (3.74 for sham IRay treatment over 12 months, compared with 4.5 injections).

An increase of 100 \( \mu \text{m} \) in foveal thickness may not accurately reflect current clinical practice as many clinicians use a lower threshold as an indication for additional anti-VEGF injections.

Due to the lack of long-term follow up, it is unclear whether radiation delivered via the IRay\textsuperscript{®} will result in additional retinal damage.

Summary of findings

The treatment of wet AMD remains a significant problem with few successful therapeutic options. The current technology brief utilised one RCT and three case series to assess whether the IRay\textsuperscript{®} Radiotherapy System is a safe and effective treatment for wet AMD. However, the included studies were limited by the extensive conflicts of interest of the study authors, the limited reporting of the nature of adverse events and the relatively short follow-up periods.

The number of adverse events attributable to the IRay system differed between the studies. Both studies by Morales-Canton et al. reported high numbers of adverse events. However, it is not entirely clear which adverse events were attributable to the IRay\textsuperscript{®} Radiotherapy System. By contrast, the RCT reported a relatively small number of adverse events attributable to the device. The most common adverse event was asymptomatic superficial punctate keratopathy, which was reported in all case series.

Results from the RCT demonstrated that there was no difference in visual acuity between the IRay 16 Gy, IRay 24 Gy and the sham group at the 12-month follow-up. In addition, the mean change in greatest CNV lesion diameter appeared to be similar between all three treatment arms. Patients in both the IRay groups required significantly fewer ranibizumab injections over 12 months, although this result may not be clinically meaningful as the mean number of injections only decreased by one. In contrast, one case series reported no change in visual acuity 12 months after IRay 16 Gy treatment, while two other case series studies reported an increase in visual acuity over the same time period in 21 and 15 patients treated with either IRay 16 Gy or 24 Gy respectively. All case series reported a decrease in mean central subfield thickness and greatest CNV lesion diameter by 12 months. However, the statistical significance of these findings was not reported. In addition, the majority of patients enrolled in the case-series required additional ranibizumab injections.
All of the included studies are expected to publish 24-month outcomes. However, studies are needed to ascertain the effect of IRay therapy on patient-relevant outcomes, such as improvement in quality of life. In addition, the appropriate dosing level and frequency of IRay treatment needs further examination, and the durability of improvements gained with this treatment over the longer term should be assessed.

**HealthPACT assessment**

There is little evidence that the addition of the IRay system to standard anti-VEGF injections confers any significant benefit to patients. The ongoing research is of low-level evidence, with similar follow-up times to the already published literature. Based on this, HealthPACT recommend that no further research on this technology be conducted on its behalf.

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

- Total number of studies: 4
- Total number of Level II studies: 1
- Total number of Level IV studies: 3

**References**


Search criteria to be used (MeSH terms)

MeSH terms: Age-related macular degeneration

Text: X-ray, Radiotherapy, stereotactic, IRay® Radiotherapy System, IRay, age-related macular degeneration, wet age-related macular degeneration, neovascular age-related macular degeneration, exudative age-related macular degeneration