Long-term visual outcomes of intravitreal ranibizumab treatment for wet age-related macular degeneration and effect on blindness rates in south-east Scotland

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Abstract

Aims To evaluate patient visual acuity outcomes and blindness rates attributable to wet AMD with a potential 5-year follow-up from intravitreal ranibizumab treatment (IVTR) in south-east Scotland.

Methods Data was analysed from 104 eyes of 96 patients who initiated treatment prior to September 2008. The main outcome measures were LogMAR visual acuity, number of clinic visits and the number of injections. Annual blind registration data in south-east Scotland were analysed using blind certifications recorded by the Royal National Institute of Blind People.

Results Patients had a mean clinical follow-up of 4 years and 1 month and a mean loss of 5.5 letters over the study period. Of the treated eyes 9.6% gained ≥ 15 letters whilst 24.0% lost ≥ 15 letters during this period. An average of 9.56 injections were administered per patient. The age-sex standardised incidence of legal blindness attributable to wet AMD in south-east Scotland peaked at 9.1 cases per 100 000 of the population in 2006 in either eye. Following the introduction of IVTR there were annual decreases in the incidence of blindness attributable to AMD falling to a trough of 4.8 cases per 100 000 of the population in 2011.

Conclusions This study demonstrates that the majority of patients in a south-east Scotland maintain their vision following IVTR in wet AMD in the real-world setting.

Our study also suggests that the introduction of IVTR has had population wide benefits in reducing the blindness attributable to wet AMD in the south-east Scotland population.

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Introduction

Wet age-related macular degeneration (AMD) is the commonest cause of blindness in the developed world.¹ It is estimated that the prevalence of blindness secondary to AMD will continue to rise owing to an ageing population.²

In the United Kingdom under the national health service (NHS) the mainstay of treatment for classic wet AMD was verteporfin photodynamic therapy (PDT) until 2007.^{3,4} Intravitreal ranibizumab (IVTR) superseded PDT as the primary treatment for all forms of wet AMD following clinical trial data which showed that long-term visual results were superior to PDT alone.^{5,6} In 2007, IVTR was licensed for treatment of new wet AMD in either eye in Scotland and an IVTR programme was instituted in south-east Scotland in September 2007.

In the United Kingdom full blindness (severe sight impairment) is defined as when wearing any corrective glasses or contact lenses patient's have a Snellen visual acuity of less than 3/60 with a full visual field, visual acuity between 3/60 and 6/60 with a severe reduction of field of

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vision, such as tunnel vision, or a visual acuity of 6/60 or above but with a very reduced field of vision with their better eye. In 1968, the Social Work (Scotland) Act gave local authorities in Scotland the power to maintain a register of people who are blind or partially sighted. However patient registration is voluntary. Certification is usually performed by an ophthalmologist who completes a certificate of vision impairment form. Scottish local authorities collate the data annually on blindness on a register. In this study only full blind (severe sight impairment) certification data was analysed. The south-east Scotland region has a population of ~950 000 people which is served by two health boards NHS Lothian and NHS Borders.

Although the efficacy of IVTR treatment has been reported in clinical trial data, there is little long-term information on efficacy in the UK clinical population. This study investigates the incidence of legal blindness attributable to wet AMD prior to and following introduction of IVTR in south-east Scotland. We also analyse the long-term IVTR clinical follow-up data.

Materials and methods

The IVTR programme in south-east Scotland was started in September 2007. All patients were initially examined clinically by an ophthalmologist, underwent ocular coherence tomography (OCT) examination and fundus fluorescein angiography (FFA). Patients were then added to a register. All macular patient's notes were kept separately and retrospectively reviewed from the register. Patients were enrolled if they had started treatment prior to September 2008 with the potential for 5 years of follow-up data. Patients who had previously been treated with PDT were excluded in order to compare outcomes to those of the clinical trials. One hundred and four eyes from 96 patients were included in the study. The main outcome measures were best corrected visual acuity measured using a standard 4 m early treatment diabetic retinopathy study LogMAR chart in an illuminated cabinet. In addition, we assessed the number of clinic visits per year and the number of injections. The type of lesion was noted from the baseline visit FFA. The normal treatment regimen in the clinic initially involved three monthly IVTR treatments over 2 months. Patients were then followed-up on a 4–8 weekly basis. Retreatment was administered if there was recurrence noted on clinical examination or OCT.

In order to assess the efficacy of the IVTR programme on blindness in the population of south-east Scotland, certification data was obtained for the same south-east Scotland population recorded by from local authority data. This population was same as that seen in the clinic. The data included patient age, gender, and cause of blindness for each eye. Only data from full blind

certification was analysed in this study. Data was tallied annually and included if the terms wet macular degeneration, exudative AMD, disciform, disciform scar, or choroidal neovascular membrane were used. We were interested in seeing if there were any changes in the blindness attributable to wet AMD immediately prior to and immediately after the introduction of the IVTR programme. We analysed the data from 2004 to 2011. During this period the primary centre for blind registration for AMD in these regions was unchanged with a stable permanent staff in the AMD and the low-vision department. In addition, blind registration criteria remained unchanged during this period. There was no change in the rate of return of blind registration forms over the period of the study.

To calculate the incidence of blindness attributable to wet AMD population estimates were taken from the general register office (Scotland). Data was collated from the mid-year estimates of populations for NHS Lothian and NHS Borders in the respective years. The data analysis for this paper was generated using the Real Statistics Resource Pack software (Release 3.5, Milan, Italy; www.real-statistics.com). The data was age and sex standardised using a European standard population to enable to comparison with other data. In addition, a time series analysis was performed using a six-point centred moving mean to investigate if blindness rates followed any trends after the introduction of the clinic.

Statement of ethics

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. The study was given ethical approval from the NHS Lothian research ethics committee with approval number 09/S1101/05.

Results

One hundred and four eyes from 96 patients were included in the study. The first patients were treated in September 2007. The mean age of patients at the start of treatment was 76 years 6 months. The cohort consisted of 104 patient eyes of which 42 were from male patients (40%) and 62 from female patients (60%). Eight patients had both eyes included in the study. Visual acuity gain/loss was recorded with a mean follow-up of 4 years 1 month. The mean visual acuity at baseline was 0.58 ± 0.28 . The final mean acuity was 0.69 ± 0.38 . Over the period of follow-up 9.6% of those treated gained ≥ 15 letters whilst 24.0% lost ≥ 15 letters.

A total of 994 injections were performed over the period of follow-up. The average number of injections per patient

was 9.56 ± 6.51 which translated to 2.35 injections per patient per year of follow-up. The mean number of clinic visits by year were 7.81 ± 3.32 for year 1, 4.84 ± 3.44 for year 2, 3.89 ± 3.58 for year 3, 2.04 ± 2.60 for year 4, and 0.43 ± 1.15 for year 5. Overall this included 2526 clinic visits an average of 24.3 per patient and 5.98 clinic visits per patient per year of follow-up. Over the 5-year period the loss to follow-up was 19% (Table 1). The only direct complications, from a total of 994 injections, were a report of one vitreous haemorrhage post-IVTR which resolved with conservative management, a single case of corneal abrasion which required 2 weeks of follow-up and topical lubricant treatment and a new sub-retinal haemorrhage post-IVTR which resolved with conservative management. No incidents of endophthalmitis were noted. To investigate whether any disparity between clinic data and trial data was owing to patient selection, we analysed the type of lesions diagnosed using angiography in our 100 cases revealed 9.6% were pure classic, 16.4% were predominantly classic, 8.7% minimally classic, 36.5% occult, and 24.0% retinal angiomatous proliferation (RAP; Table 2)

Analysis of the blind registration data revealed that the incidence of legal blindness attributable to wet AMD in the population of south-east Scotland peaked at 9.9 cases per 100 000 in 2004. A trough of 3.7 cases per 100 000 was found in 2011. This corresponds to a peak to trough reduction of 60.6%. Following age-sex standardisation the incidence of legal blindness attributable to wet AMD in south-east Scotland peaked at 9.1 cases per 100 000 in 2006 in the entire south-East Scotland population.

Following the introduction of IVTR there were annual decreases in the incidence of blindness attributable to AMD. Cases fell to a trough of 4.8 cases per 100 000 in the south-east Scotland population in 2011 in either eye. This is a drop of 47% from the peak level (Table 3; Figure 1).

In order to more accurately assess trends in overall blindness statistics in the region following the introduction of the IVTR programme a time series analysis was performed. The analysis showed a decrease in blind registrations with time since the introduction of the IVTR programme. Overall this model showed a moderate correlation of reduced blindness with time in the population since the programme was introduced. ($r^2 = 0.76$; Figure 2).

Discussion

Our study reports on actual outpatient clinic data for patients undergoing IVTR for wet AMD. The information in this study is set against a background of clinical trial data investigating the efficacy of IVTR in wet AMD. The two landmark clinical trials for the treatment of wet AMD using ranibizumab were the MARINA for minimally classic/occult disease and ANCHOR for predominantly classic disease. The number of patients who had lost ≥ 15 letters VA in the MARINA⁵ and ANCHOR trials were 9 and 10%, respectively.⁶ Whereas 30% of ranibizumab-treated patients from MARINA and 38% of ranibizumab-treated patients from ANCHOR had gained ≥ 15 letters VA. In this study 24% of patients had lost ≥ 15 letters whereas only 10% of those treated gained ≥ 15

Table 1 Summary statistics for clinic data

Average follow-up length	4 years 1 month	Range (3 months to 5 years 1 month)
Mean visual change (logMAR)	0.11	SD 0.36
Mean number of injections per patient during the follow-up period	9.61	SD 6.49
Mean number of injections per patient per year of follow-up	2.35	
Mean number of clinic visits	24.30	SD 10.4
Mean follow-up clinic visits per year of follow-up	5.98	

Table 2 Visual acuity with lesion type diagnosed by FFA

Lesion type	Count	Percent of total	VA start mean (LogMAR)	VA final mean (LogMAR)	VA difference mean (LogMAR)	VA start SD	VA final SD	VA change SD
Classic	10	9.6	0.74	0.92	0.18	0.28	0.52	0.40
PC	17	16.4	0.68	0.71	0.03	0.30	0.38	0.36
MC	9	8.7	0.61	0.77	0.16	0.21	0.32	0.36
Occult	38	36.5	0.47	0.59	0.12	0.28	0.37	0.37
RAP	25	24.0	0.62	0.73	0.12	0.23	0.36	0.33
Unknown	5	4.8	0.50	0.48	-0.02	0.28	0.25	0.19
Total	104	100						

Table 3 Crude and age-sex standardised incidences of blindness owing to wet AMD in the entire south-east Scotland population

Year	Mid-year population for SE Scotland	Blind registrations due to wet AMD in either eye	Age-sex standardised blind registration for wet AMD in either eye	Crude incidence of blindness attributable to wet AMD in either eye per 100 000	Age-sex standardised incidence of blindness secondary to wet AMD in either eye per 100 000
2004	896 774	85	75.8	9.5	8.5
2005	902 323	79	77.6	8.8	8.6
2006	911 557	81	82.6	8.9	9.1
2007	921 194	78	80.7	8.5	8.8
2008	930 157	56	65.8	6.0	7.1
2009	938 911	50	63.8	5.3	6.8
2010	949 581	41	46.8	4.3	4.9
2011	961 877	36	46.4	3.7	4.8

Figure 1 Graph showing the age-sex standardised figures for registered blindness by year in south-east Scotland. The vertical line indicates the start the introduction to the IVTR programme.

letters during the follow-up period. Our figures are worse than those reported in these clinical trials. However, both these studies provided an initial report at 2-year follow-up compared with an average of ~4 years follow-up in this study. Consequently the data are not directly comparable. There are relatively few studies which report follow-up results with >2 years follow-up. The HORIZON study provided a 2-year extension for patients previously enrolled 2-year prospective studies for ranibizumab.⁷ In the ranibizumab-treated group after 4 years there was a mean loss of 0.1 letters. In our study the mean loss was 0.55 letters.

There was a drop in vision once as required dosing was started. This suggested under treatment of patients in the HORIZON study who lost a mean of seven letters from switch to as required dosing. Under treatment may also be the case for patients in this study who were treated on an as required basis throughout follow-up with the exception of the loading phase. The risk of as required treatment scheduling is further highlighted by a recent retrospective study which has reported on long-term outcomes for fixed-interval dosing of anti-VEGF treatment approximately every 4–8 weeks. The eyes were predominantly treated with IVTR although aflibercept

Figure 2 Time series analysis using centred moving means to calculate a trendline for overall registered blindness in south-east Scotland since the introduction of the IVTR programme.

and bevacizumab were used in a minority of cases. The 5-year visual outcomes reported a mean gain of 14 letters. The patients in this study were treated with a mean of 10.5 injections per year. This is comparable to only 2.2 injections per year during the HORIZON study in the ranibizumab group and only 2.35 injections per patient per year in this study. Results from the PIER study have shown that less frequent follow-up and treatments are associated with poorer outcomes.⁸

The proportion of different types of angiographically identified lesions were similar in this study to other reported studies for populations showing occult lesions as the most common form identified angiographically for patients with wet AMD.^{9,10} Cohen *et al.*⁹ found a total of 17.6% had classic CNV only, 5.4% and 8.3% had predominantly and minimally classic CNV, respectively, and 32.7% had occult CNV. RAP was observed in 15.1% of cases. As has been noted previously overall predominantly or minimally classic diagnosis was associated with a significantly poorer initial visual acuity when compared with occult ($P=0.0025$).¹¹ Our results

showed that patients with predominantly classic lesions lost the fewest letters over the study period. However, this was not found to be statistically significant when compared with other types of neovascular lesions. In order to reduce the effect of age-sex variation in our regional population we age-sex standardised incidences to a standard European population. The analysis showed that the fall in crude incidences for blindness was sustained even following standardisation.

The first IVTR treatments for AMD took place in September 2007 in south-east Scotland. Our findings from blind registration data suggest that blindness attributable to wet AMD have reduced significantly following the introduction of IVTR. Looking at overall figures for blindness these have shown a consistent decrease until 2011. The proportion of blindness attributable to AMD peaked at 39.4% in 2006 and has steadily declined to 21.1% in 2011. Meanwhile there is a background of steadily decreasing blindness attributable to other causes of blindness such as glaucoma (data not shown). These figures suggest a link between the inception of IVTR treatment in south-east Scotland and the decline in blindness attributable to wet AMD. Following the introduction of IVTR there were annual decreases in the incidence of blindness attributable to AMD falling to a trough of 4.8 cases per 100 000 in 2011 in either eye. This is a drop of 47% from the peak level. The peak-trough figure allows a comparison with other data sets from similar populations in industrialised nations. A recent study describing the Danish population showed a reduction of half in the yearly registrations for blindness owing to wet AMD in persons aged over 50.¹² A study of the non-Hispanic white population in the US estimated that the incidence of legal blindness would fall by 72% if monthly ranibizumab injections were given for a 24-month period.¹³ The accuracy of blind registration data may have been limited by potential under registration by ophthalmologists. It has been well documented that ophthalmic practitioners variably register patients despite eligibility criteria being met.^{14–16} However, during the period of this study the reporting criteria for blindness have remained unchanged and the staff registering patients have remained which should reduce the variability in the figures.

In summary, the long-term follow-up data presented in this study suggests that IVTR treatment shows that although visual outcomes do not match fixed-regime dosing clinical trial results the data does demonstrate clinical real-world efficacy in maintaining long-term vision in patients treated with IVTR for wet AMD in south-east Scotland. In addition the introduction of the IVTR programme in south-east Scotland appears to have resulted in a reduction in blindness attributable to wet AMD in the region.

Summary

What was known before

- Intravitreal ranibizumab therapy in clinical trials (ANCHOR/MARINA) is effective in maintaining and improving vision in the treatment of wet age-related macular degeneration (AMD).

What this study adds

- Real world data from our study shows that with long-term follow-up of 4 years there is a slight loss of visual acuity in the treatment of wet AMD but there is a significant fall in blind registration rates attributable to this condition.

Conflict of interest

The authors declare no conflict of interest.

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Authors contributions

The study was proposed and designed by PC and MG. Data collection was performed by SB, SJ, AA and DO. SB and SJ carried out the write up. Editing was performed by BD and PC.

Disclaimer

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