Changes in intraocular pressure in study and fellow eyes in the IVAN trial

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ABSTRACT
Purpose To describe changes in intraocular pressure (IOP) in the ‘alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)’ trial (registered as ISRCTN92166560).

Design Randomised controlled clinical trial with factorial design.

Participants Patients (n=610) with treatment naïve neovascular age-related macular degeneration were enrolled and randomly assigned to receive either ranibizumab or bevacizumab and to two regimens, namely monthly (continuous) or as needed (discontinuous) treatment.

Methods At monthly visits, IOP was measured preinjection in both eyes, and postinjection in the study eye.

Outcome measures The effects of 10 prespecified covariates on preinjection IOP, change in IOP (postinjection minus preinjection) and the difference in preinjection IOP between the two eyes were examined.

Results For every month in trial, there was a statistically significant rise in both the preinjection IOP and the change in IOP postinjection during the time in the trial (estimate 0.02 mm Hg, 95% CI 0.01 to 0.03, p<0.001 and 0.03 mm Hg, 95% CI 0.01 to 0.04, p<0.002, respectively). There was also a small but significant increase during the time in trial in the difference in IOP between the two eyes (estimate 0.01 mm Hg, 95% CI 0.005 to 0.02, p<0.001). There were no differences between bevacizumab and ranibizumab for any of the three outcomes (p=0.93, p=0.22 and p=0.87, respectively).

Conclusions Anti-vascular endothelial growth factor agents induce increases in IOP of small and uncertain clinical significance.

Trial registration number ISRCTN92166560.

INTRODUCTION
A rise in intraocular pressure (IOP) was not observed in the initial ANCHOR and MARINA trials of agents that inhibit vascular endothelial growth factor (VEGF); but subsequently small clinical series have reported rises in IOP in around 3%1,2 to 12%3 in treated eyes with similar rates observed in the fellow eye.4 Concerns have been raised that there is a cumulative effect on pressure rise after multiple intraocular injections of anti-VEGF agents,5,5 although this finding has not been consistently replicated.9 Mechanisms that have been postulated to explain this IOP rise include the volume effect of the injection,9 the particular properties of the agent (bevacizumab is a full length antibody with an Fc fragment which may induce a trabeculitis,10–12 and/or the presence of particulates) or the inhibition of VEGF within the trabecular meshwork leading to reduced facility of aqueous outflow.

Accordingly, we undertook an exploratory analysis of the alternative treatments in the inhibition of VEGF in age-related choroidal neovascularisation (IVAN) clinical trial dataset. The IVAN trial (registered ISRCTN92166560) was a randomised controlled trial with a 2×2 factorial design comparing ranibizumab with bevacizumab and monthly (continuous) with as needed (discontinuous) treatment strategies.

We hypothesised that:

- Preinjection IOP would increase with the number of injections administered.
- The size of the postinjection pressure ‘spike’ would provide an estimate of the functioning of the trabecular meshwork and facility of aqueous outflow.

As IOP was measured in both eyes at every visit, the difference in IOP between study and fellow eyes over time could also be examined, allowing the fellow eye to act as a within-subject control for a trend in preinjection IOP.

MATERIALS AND METHODS

Patients Patients over the age of 50 with active, treatment naïve neovascular age-related macular degeneration (nAMD) were recruited. Those with field defects attributable to glaucoma were excluded (guidance rather than formal exclusion—there being no reliable way to distinguish field defects due to glaucoma from those due to macular degeneration) but those with a history of ocular hypertension, or glaucoma per se, were not (ie, these patients are best considered as having preperimetric glaucoma). The CONSORT diagram is reported elsewhere.13

The full list of inclusion and exclusion criteria is provided as online supplementary file 1. A UK National Health Service Research Ethics Committee approved the trial (07/NIR03/37). Patients with glaucoma were identified on the basis of either having had glaucoma surgery (of which there were none) or prescription of topical pressure lowering medications (46 patients). This criterion does not distinguish between patients with ocular hypertension and those with glaucoma and so these two groups were combined into a single group and labelled as glaucoma for the analyses. And it should be noted that neither gonioscopy nor central corneal thickness measurements were performed.
IOP measurements
The IOP was measured monthly using Goldmann applanation tonometry in both eyes prior to treatment and in the study eye after injection if treated. Two readings were made and if more than 2 mm apart, a third reading was taken. Visit IOP for each eye was the mean of the two or the median of the three. Equipment was calibrated at least twice annually.

The clinicians were not masked to which was the study eye for these measurements but were doing it for safety monitoring only and no hypothesis was even discussed until after data collection was complete.

Study outcomes
Three outcomes were prespecified in an analysis plan. These were as follows:
1. Postinjection IOP ‘spike’ (ie, postinjection IOP minus preinjection IOP) in the study eye, at visits where injections were administered.
2. Preinjection IOP in the study eye.
3. The difference in preinjection IOP between the study and fellow eyes (ie, study eye preinjection IOP minus fellow eye preinjection IOP).

Statistical analysis
The analyses used data from all available IVAN study visits (up to 25 visits). Ten covariates were prespecified in the analysis plan: months in study, months since last injection, mean arterial blood pressure, study drug, cataract surgery, glaucoma, age at randomisation, gender, baseline preinjection IOP in the study eye (outcomes 1 and 3) and the time between the injection and the postinjection IOP measurement (outcome 1). We treated time in trial as a proxy for number of injections (adjusting for time since last injection) since the two were strongly correlated. Linear mixed modelling was used to analyse the three study outcomes; intercept and ‘months in trial’ terms were fitted as random effects in all three models. For the analyses of preinjection IOP, namely outcomes 2 and 3, the baseline measurements of each outcome were modelled jointly with the subsequent values to avoid the need to exclude cases with missing baseline values. Model validity was checked and outlying values were excluded. Linearity assumptions were also checked and when non-linear, the data were grouped into categories. All covariates were retained in the models regardless of their significance. Results are reported as effect estimates with 95% CIs. Two-sided p values < 0.05 are considered statistically significant.

IOP was measured at every visit and the amount of missing data was low (less than 5% of attended visits; a further 13% of visits were not attended). However, blood pressure was only measured every 3 months. Plots of the mean arterial pressure suggested that the pressure did not change much over time, so values were interpolated for the visits where it was not measured.

Cataract surgery was identified by the phakic status of the eye. A time-dependent indicator variable was fitted to denote when surgery took place. The impact of having surgery in both eyes was tested by adding an interaction term to the model. This term was retained if significant at the 5% level. As for cataract surgery, a time-dependent indicator variable was fitted to describe when patients’ were identified as glaucomatous during time in the trial.

Baseline preinjection IOP in the study eye, study drug, age at randomisation and gender did not vary across visits.

RESULTS
All 610 participants in the IVAN study cohort were included in this analysis. There were 13 371 study visits including baseline and injections were administered at 10 160 of these visits.

The median duration of active participation in the trial was 23.6 months (IQR 22.8 to 24.3), with a median time between injections of 1.0 month (IQR 0.9 to 1.2). Baseline preinjection IOP in the study eye was measured for 607/610 patients with a median of 15 mm Hg (IQR 14 to 18). Glaucoma was present in 46/610 (7.5%) patients, and 219/610 (35.9%) patients were pseudophakic/aphakic in at least one eye during the trial; the majority of patients classified as glaucomatous (37/46 (80.4%) or pseudophakic/aphakic (181/219 (82.6%)) were classified as such at trial entry. Participant demographics and ophthalmic characteristics are summarised in table 1.

Participant age at randomisation was grouped into categories as the relationship with outcomes was non-linear.

Outcome 1: spikes in postinjection IOP (postinjection IOP minus preinjection IOP)
IOP was measured preinjection and postinjection for 10 009 of the 10 160 (98.5%) injections and the median postinjection IOP spike was +3 mm Hg (IQR 0 to 7).

Figure 1 shows the multivariable effect estimates (ie, adjusted for other covariates in the model) for the covariates in the model examining the factors associated with postinjection IOP spike.

For every month in the trial, on average a patient’s postinjection IOP increased by 0.03 mm Hg (95% CI 0.01 to 0.04, p = 0.002). In addition, the longer the time interval between injection administration and measurement of postinjection IOP, the lower the IOP spike (−0.07 mm Hg/min).

Compared with no cataract surgery, the IOP spike was reduced in cataract-operated study eyes (−1.00 mm Hg, 95% CI −1.75 to −0.25), but did not differ when fellow eyes only or both eyes had experienced surgery (figure 1; test for eye interaction p = 0.028).

Glaucoma in either eye increased the postinjection IOP spike on average by 1.15 mm Hg. The relationship with age was non-linear, but those aged 85 and above had the highest IOP spike compared with the reference group of age 50–69 years.

Male patients had a larger postinjection IOP spike than females.

Months since last injection, mean arterial pressure and study drug had no statistically significant effect on postinjection IOP change and the use of bevacizumab resulted in a non-significant but lower IOP spike than ranibizumab.

Outcome 2: preinjection IOP in the study eye during time in study
IOP in the study eye was measured prior to injection at 13 281 (99.3%) of the 13 371 attended study visits. Data were available for 607 patients at visit 0 and 514 patients at visit 24. The median preinjection IOP across all visits was 15 mm Hg (IQR 13 to 18). Figure 2 shows the multivariable effect estimates for covariates associated with preinjection IOP.

The average preinjection IOP in the study eye increased by 0.02 mm Hg/month. For every unit increase of mean arterial pressure, preinjection IOP increased by 0.01 mm Hg. Compared with no cataract surgery, study eye surgery significantly reduced preinjection IOP (−1.42 mm Hg), as did surgery on both eyes (−0.79 mm Hg), but surgery on the fellow eye alone had no effect (−0.18 mm Hg; test for eye interaction p = 0.028).

Months since last injection, study drug, glaucoma status and gender had no statistically significant effect on preinjection IOP (p = 0.76, p = 0.93, p = 0.47 and p = 0.32, respectively).
### Table 1  Summary of description of study population by glaucoma status

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>n</th>
<th>Glaucoma (n=46)</th>
<th>No glaucoma (n=564)</th>
<th>Overall (n=610)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (Avastin)</td>
<td>610</td>
<td>23 (50.0%)</td>
<td>273 (48.4%)</td>
<td>296 (48.5%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>610</td>
<td>80.0 (7.1)</td>
<td>77.5 (7.4)</td>
<td>77.7 (7.4)</td>
</tr>
<tr>
<td>50–69</td>
<td>2</td>
<td>2 (4.3%)</td>
<td>90 (16.0%)</td>
<td>12 (1.9%)</td>
</tr>
<tr>
<td>70–74</td>
<td>13</td>
<td>28.3%</td>
<td>97 (17.2%)</td>
<td>110 (18.0%)</td>
</tr>
<tr>
<td>75–79</td>
<td>8</td>
<td>17.4%</td>
<td>151 (26.8%)</td>
<td>159 (26.1%)</td>
</tr>
<tr>
<td>80–84</td>
<td>7</td>
<td>15.2%</td>
<td>132 (23.4%)</td>
<td>139 (22.8%)</td>
</tr>
<tr>
<td>85+</td>
<td>16</td>
<td>34.8%</td>
<td>94 (16.7%)</td>
<td>110 (18.0%)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>610</td>
<td>18 (39.1%)</td>
<td>226 (40.1%)</td>
<td>244 (40.0%)</td>
</tr>
<tr>
<td>Preinjection IOP in study eye</td>
<td>607</td>
<td>16.8 (3.8)</td>
<td>15.3 (3.1)</td>
<td>15.4 (3.2)</td>
</tr>
<tr>
<td>Postinjection IOP change in study eye</td>
<td>594</td>
<td>2.8 (6.5)</td>
<td>3.1 (5.6)</td>
<td>3.1 (5.7)</td>
</tr>
<tr>
<td>Preinjection IOP eye difference (study eye IOP minus fellow eye IOP)</td>
<td>606</td>
<td>-0.7 (3.8)</td>
<td>0.0 (1.6)</td>
<td>-0.1 (1.9)</td>
</tr>
<tr>
<td><strong>During the trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cataract surgery (pseudo/aphakic)</td>
<td>610</td>
<td>27 (58.7%)</td>
<td>192 (34.0%)</td>
<td>219 (35.9%)</td>
</tr>
<tr>
<td>In study eye only</td>
<td>7</td>
<td>7 (25.9%)</td>
<td>39 (20.3%)</td>
<td>46 (21.0%)</td>
</tr>
<tr>
<td>In fellow eye only</td>
<td>3</td>
<td>11.1%</td>
<td>29 (15.1%)</td>
<td>32 (14.6%)</td>
</tr>
<tr>
<td>In both eyes</td>
<td>17</td>
<td>63.0%</td>
<td>124 (64.6%)</td>
<td>141 (64.4%)</td>
</tr>
<tr>
<td>Months in trial</td>
<td>610</td>
<td>23.5 (23.0 to 24.5)</td>
<td>23.6 (22.8 to 24.3)</td>
<td>23.6 (22.8 to 24.3)</td>
</tr>
<tr>
<td>Months between injections</td>
<td>13,371</td>
<td>1.0 (0.9 to 1.8)</td>
<td>1.0 (0.9 to 1.2)</td>
<td>1.0 (0.9 to 1.2)</td>
</tr>
<tr>
<td>Time (min) between injection and postinjection IOP measurement</td>
<td>9966</td>
<td>25 (15 to 33)</td>
<td>21 (12 to 32)</td>
<td>22 (13 to 32)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>4795</td>
<td>95.4 (10.6)</td>
<td>96.3 (10.9)</td>
<td>96.2 (10.9)</td>
</tr>
<tr>
<td>Preinjection IOP in study eye</td>
<td>13,281</td>
<td>16.6 (4.0)</td>
<td>15.3 (3.3)</td>
<td>15.4 (3.4)</td>
</tr>
<tr>
<td>Postinjection IOP change in study eye</td>
<td>10,009</td>
<td>4.4 (6.9)</td>
<td>3.8 (5.3)</td>
<td>3.8 (5.4)</td>
</tr>
<tr>
<td>Preinjection IOP eye difference (study eye IOP minus fellow eye IOP)</td>
<td>13,208</td>
<td>-0.4 (5.0)</td>
<td>0.1 (1.8)</td>
<td>0.5 (2.3)</td>
</tr>
<tr>
<td>At visit 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection IOP in study eye</td>
<td>514</td>
<td>17.0 (4.0)</td>
<td>15.7 (3.3)</td>
<td>15.8 (3.3)</td>
</tr>
<tr>
<td>Postinjection IOP change in study eye (at visit 24)</td>
<td>358</td>
<td>5.1 (4.1)</td>
<td>3.9 (5.1)</td>
<td>4.0 (5.0)</td>
</tr>
<tr>
<td>Preinjection IOP eye difference (study eye IOP minus fellow eye IOP)</td>
<td>510</td>
<td>0.5 (2.2)</td>
<td>0.2 (1.9)</td>
<td>0.2 (1.9)</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure.

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**Figure 1**  Model for spikes in postinjection IOP (postinjection minus preinjection) in the study eye. Plot of the effects of covariates on IOP spikes in injected study eyes. The point estimates and 95% CIs are shown. FE, fellow eye; IOP, intraocular pressure; OU, both eyes; SE, study eye.
Outcome 3: difference in preinjection IOP between study and fellow eyes during time in study (study eye minus fellow eye)

Preinjection IOP was measured in both eyes for 13,208 (98.8%) of the 13,371 attended study visits. Data were available for 606 patients at visit 0 and 510 patients at visit 24.

Figure 2 Model for preinjection IOP in the study eye. Plot of the effects of covariates on preinjection IOP in the study eye. The point estimates and 95% CIs are shown. FE, fellow eye; IOP, intraocular pressure; OU, both eyes; SE, study eye.

Figure 3 shows the multivariable effect estimates of the covariates. The difference between IOP in the two eyes increased over time (0.01 mm Hg/month) with higher readings from the study eye compared with the fellow eye. Longer time intervals between injections reduced the difference in IOP between the study and fellow eye (−0.02 mm Hg). Cataract surgery on the
surprise that this was not observed. The IVAN trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 07/36/01). The views and opinions expressed are those of the authors and do not necessarily reflect those of the Health Technology Assessment programme, National Institute for Health Research, the UK National Health Service, or the Department of Health. The contributors All authors have read and approved this manuscript. UC was the lead investigator. FG, JG and A/JEF were all trial investigators. BCR, CAR and DMLJS are all members of the trials unit that run the trial. The data analysis for this paper was performed by DMLJS and supervised by CAR and BCR. The manuscript was written by AJEF and approved by all authors.

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