Intravitreal Anti-VEGF Therapy for Neovascular Age-Related Macular Degeneration and the Risk of Stroke

Abstract:
CA Cleary, D Sharaznayan, M Hickey-Dwyer
Department of Ophthalmology, Mid-Western Regional Hospital, Dooradoyle, Limerick

The purpose of this study was to compare the vascular event rate in AMD patients treated with an intravitreal VEGF inhibitor with a historical control group treated with photodynamic therapy. We reviewed medical records of 83 patients treated with intravitreal anti-VEGF for AMD between 2005-2007, and 60 patients treated with PDT between 2001-2004. Mean follow-up in the anti-VEGF group was 40 months versus 95 months in the PDT group. Mean age (76–9 years, versus 74–10 years, p=n.s.) and cardiovascular risk factor profile were similar. Vascular event rates in each group were 2.6 per 100 patient years versus 2.3 per 100 patient years, (p = n.s). Age over 80 years was associated with an increased risk of a vascular event (odds ratio=1.113, p<0.05). Despite the high prevalence of risk factors in AMD patients, the incidence of vascular events was low and associated with older age rather than therapy received.

Introduction
Since 2005 intravitreal anti-VEGF (Vascular Endothelial Growth Factor) therapies have been used worldwide for the treatment of neovascular Age-related Macular Degeneration (AMD) and the reported incidence of adverse events is low. Nevertheless concerns persist among retinal specialists that these therapies may increase the risk of stroke. The ANCHOR trial of intravitreal anti-VEGF therapy (ranibizumab) for the treatment of AMD reported a trend towards an increased incidence of arterial thromboembolism (4.3% compared with 2.1% in the PDT-treated group) after 1 year a trend that was no longer evident at two years follow-up. We wanted to examine whether the rate of vascular events increases several years after anti-VEGF therapy. Therefore we compared the cardiovascular risk profile and long-term clinical course of patients who received photodynamic therapy (PDT) between 2001 and 2004 with those who received anti-VEGF therapy between 2005 and 2007.

Methods
Patients were recruited from the specialist retina clinic in the city of Limerick, Ireland, which is based in a regional hospital which provides comprehensive medical care to a population of 360,000. Using medical records, consultation with general practitioners (100 GPs conducted telephone interviews as a method of follow-up) and death certification records, we conducted a retrospective review of neovascular AMD patients treated with intravitreal bevacizumab between 2005 and 2007, and patients treated with PDT between 2001 and 2004. This study complied with the tenets of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Midwestern Regional Hospital Limerick.

The following data were collected for each patient: indication for treatment; number of treatments, systemic adverse events, baseline cardiovascular risk factors including age, gender, blood pressure measurements, hypertension, diabetes, cardiac disease, peripheral vascular disease, smoking, previous thrombotic stroke or transient ischaemic attack (TIA), and hypercholesterolaemia. Arterial thrombo-embolic events were evaluated using the Antiplatelet Trialists Collaboration (APTC) criteria, which defines an event as a nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death owing to vascular or unknown causes recently attended the clinic, up to date information on their medical status was obtained from telephone interviews with their GP.

Statistical analysis was performed using Microsoft Excel, Graphpad Prism and SPSS statistical software programs. To allow for variations in follow-up time, event rates per 100 patient years were calculated using the formula: Events per 100 Patient-Years = (Number of events/ sum of exposure time of all patients) x 100. Unpaired students t-tests were
used to examine for baseline differences in demographics and risk factors. Kaplan-Meier curves were used to compare differences in event rates. Logistic regression and Chi-squared tests were used to examine for associations between baseline risk factors and vascular events. Linear regression was used to examine the relationship between age and vascular events.

Results
The medical records of 83 neovascular AMD patients treated with anti-VEGF therapy and 60 patients treated with PDT were reviewed. The mean number of injections in the bevacizumab group was 2.5 per patient (range 1 to 8, each injection contained 2.5 mg bevacizumab). Seventeen patients in the bevacizumab group later received treatment with intravitreal ranibizumab. In this group, the mean number of ranibizumab injections per patient was 2.5 (range 1 to 7 injections, each injection contained 0.5 mg ranibizumab). Twenty-two patients in the anti-VEGF group also received treatment with PDT (in this subgroup, the mean number of treatments per patient was 2.2; range: 1 to 8). None of the patients in the historical PDT control group received anti-VEGF therapy. The mean number of PDT treatments in this group was 2.7 (range: 1 to 8).

Figure 1. Systemic vascular events and causes of death in neovascular AMD patients treated with PDT or anti-VEGF therapy.

The mean follow-up in the bevacizumab group was 40 months (median =42 months; range 20 to 51 months), and in the PDT group was 95 months (median = 97 months; range 73 to 109 months). The ages of the two groups at the time of first treatment were similar, 76–9 years in the anti-VEGF group versus 74–10 years in the PDT group, (p = ns). There was no difference in the rate of systemic adverse events between the anti-VEGF and PDT groups. All but one vascular event occurred in patients over 80 years old, and advanced age was the only risk factor significantly associated with increased stroke risk. Linear regression demonstrated a relationship between increasing age and systemic vascular events in both the anti-VEGF (r²=0.75, slope=0.33+/–0.19) and PDT groups (r²=0.48, slope=0.103+/–0.107).
We recorded cardiovascular risk profiles in both groups (Table 1). Many patients had uncontrolled hypertension: 53% of the anti-VEGF group and 32% in the PDT group had systolic blood pressures greater than 140 at baseline and almost one-third of patients treated with anti-VEGF had systolic blood pressures greater than 160 at baseline. We did not observe a change in mean systolic or diastolic BP readings during the course of intravitreal anti-VEGF therapy, and we found no relationship between hypertension and systemic vascular events (Table 3). More patients in the anti-VEGF group were on aspirin (42% versus 15% in the PDT group, p<0.001) while patients in the PDT group were more likely to take a vitamin K antagonist (10% versus 1% in the anti-VEGF group, p<0.05).

**Discussion**

Anti-VEGF therapy for AMD has been in use for 5 years, however the question of whether it increases the risk of stroke...
Most studies of anti-VEGF therapy are designed to detect differences in efficacy rather than patient safety. Based on the event rate in this study we estimate it would require a controlled study of 2,000 subjects per group to detect a significant difference in vascular event rates over 3 years. Given the clinical efficacy of anti-VEGF injections, it would not be unreasonable to enroll large numbers of patients into a placebo-controlled safety study. Therefore, we performed a retrospective study, the principal advantage of which is that we can quickly make use of data about rare events that have already been collected, rather than waiting many years for the completion of a prospective study. Generally, the main disadvantage of retrospective studies is that the investigator has no control over how the data were collected and it can be impossible to know whether the data are biased or incomplete. This does not apply to our study, where the investigators are based in a regional centre of medical care for this patient population, and most patients remain under our care. While we might have underestimated the total number of vascular events (because clinically silent events can be detected only by routine testing in a prospective study), we believe that we have captured clinically important vascular events after AMD therapy.

Another disadvantage of retrospective studies is that comparison populations can be dissimilar. In this study both groups come from the same clinic population and geographic area, and had similar age and risk factor profiles, and patients received different therapies based exclusively on the year they attended clinic. We cannot comment whether undetermined factors could have changed the frequency of stroke between 2001 and 2009. Caution has to be exercised in making inferences about associations between disease frequencies from retrospective studies. Our data failed to show an increased stroke rate with the use of anti-VEGF therapy, although we accept that this could be due to a type 2 error (because of the low event rate).

The greatest risk factors for thrombotic stroke are advanced age and a history of prior stroke or TIA. In this study the incidence of vascular events appears to lie in the lower range of that expected for the age and risk profile, possibly because very few patients with a history of stroke or TIA were treated. This may represent a selection bias against treating patients perceived to be higher risk, or may reflect that patients suffering the sequelae of a stroke are less likely to seek treatment for AMD. A large retrospective study of 15,771 neovascular AMD patients reported an annualised incidence of ischaemic CVA of 3.5% and 3.6% respectively, and stroke rate increased with increasing age from 1.2% in the 65-69 year-olds to 4.7% in the over 85s. In our study all but one event occurred in patients over 80. Based on these results and on the ANCHOR report, we expected an incidence of ischaemic stroke above 4.0% in our anti-VEGF group if stroke risk was increased, however we found an incidence of only 2.6%. Our failure to detect an increased stroke rate in patients who receive anti-VEGF therapy is consistent with other studies which reported no increase in vascular events following intravitreal bevacizumab treatment for a variety of indications.

We acknowledge the limitations of this study, including the small numbers and retrospective design. We cannot conclusively answer the question of whether intravitreal anti-VEGF therapy increases stroke risk. Treatment regimens with intravitreal anti-VEGF agents have become more intensive since the patients in this study were treated. In 2005, off-label bevacizumab use had just begun, and injections were performed as needed, hence the number of injections was fewer than patients receive now. One-third of patients in this study also received PDT therapy, which reduced the number of injections. However patients in this study received the higher 2.5mg dose rather than the 1.25mg dose of bevacizumab, and the correspondingly higher dose (0.5mg) of ranibizumab, which potentially might increase stroke risk, but this was not shown to be the case.

VEGF inhibitors could cause cerebrovascular events by elevating systemic blood pressure or by damaging the cerebral vascular endothelium. Anti-VEGF agents injected intravascularly enter the systemic circulation in much lower concentrations compared to intravenous dosing during cancer therapy. While increased blood pressure has been reported in cancer patients treated with intravenous bevacizumab, and patients receiving bevacizumab are at increased risk of arterial thromboembolism (5.5 events per 100 person years compared with 3.1 events per 100 patient years for cancer patients not on bevacizumab). The risk of arterial thromboembolic events in cancer patients was also associated with older age (greater than 65 years). It is difficult to counsel an older patient with wet AMD about systemic risks of receiving intravitreal anti-VEGF therapy, however it may be prudent to advise patients with a history of stroke, TIA or multiple risk factors about the theoretically increased risk of stroke associated with this therapy. In conclusion, we found that intravitreal anti-VEGF therapy do not appear to increase stroke risk in an Irish AMD population within a 3-year follow-up period. Age, rather than choice of therapy was the only predictor of increased stroke risk in this population.
References


