Aim: To evaluate eyes with AMD that responded poorly to anti VEGF therapy and study reasons for treatment failure.

Methods: 52 eyes that received anti VEGF therapy (PRONTO schedule) and completed 1 year follow up and showed poor response (loss of > 2 lines) were analyzed. Non-responders were defined as no change in fluid/vision after 3 loading injections. Tachyphylaxis was defined as early response to treatment but recurrence of fluid and diminishing response to further therapy.

Results: Of eyes with poor response, in 24 eyes (46.2%) the primary diagnosis of AMD needed revision. This group included PCV (19), RAP (4) and Vitelliform lesion (1). After excluding the mistaken diagnoses there were 14 eyes (26.9%) who were non-responders and 11 eyes (22.2%) which showed tachyphylaxis. 6 eyes (11.5%) had complications like RIP, scarring, RPE atrophy and poor visual outcome.

Conclusion: Poor response to anti VEGF may be due to various factors. In nearly 50% the diagnosis of AMD may be mistaken of which PCV is a major pathology. Non-responders and tachyphylaxis account for another 50% cases and these may require treatment modifications. Considering the systemic risks and cost of therapy involved identification of these eyes is very essential.

Introduction

The treatment of choroidal neovascularisation (CNVM) has changed considerably with the introduction of intravitreal anti vascular endothelial growth factor (VEGF) agents. In 2004 Gragoudas et al. showed that pegaptanib (Macugen), which binds one isoform of VEGF (VEGF 165), was able to reduce the risk of visual loss in patients with CNVM while a small percentage of patients gained or remained stable. More recent reports on other pan-VEGF agents (ranibizumab, Lucentis) have proven that long term improvement in visual acuity is possible. Initial reports on the intravitreal use of bevacizumab (Avastin), a full-size antibody related to ranibizumab, in patients with CNVM have demonstrated a beneficial morphological and functional outcome and off-label use of bevacizumab has also gained popularity. Studies have also demonstrated the beneficial effects of anti VEGF agents following a loading dose schedule followed by an OCT based SOS therapy (PRONTO). Compared with previous treatment modalities such as photodynamic therapy (PDT), which caused vision stabilisation but rarely demonstrated an improvement of visual acuity, anti-VEGF agents have raised the standards of treatment and can improve visual acuity. The proportion of patients with improving visual acuity has ranged from 28% to 43%. So far it is not known why more than half of patients do not improve after anti VEGF therapy and cannot be considered as poor responders. In this retrospective study we investigated the causes of treatment failures in eyes that received anti VEGF agents.

Aim

The aim of this study is to evaluate eyes with AMD that responded poorly to anti VEGF therapy and study reasons for treatment failure.

Materials And Methods

This was a retrospective study involving eyes that were diagnosed as having wet ARM and treated with anti VEGF monotherapy at Chaithanya Eye Hospital and Research Institute, Trivandrum between January 2007 and December 2008. The diagnosis of wet ARM was made on the basis of clinical examination with indirect ophthalmoscopy, 78 D examination and fundus fluorescein angiography. All eyes were treated similar to the PRONTO schedule with 3 loading doses of pan VEGF blockade at 4 weekly intervals. Following the loading dose these patients were followed up at monthly intervals for 1 year. Best corrected visual acuity and reading ability at baseline and at each follow-up examination were recorded. A note of systemic complications if any was also recorded. Patients who had evidence of persistent activity or recurrence were treated with the same anti VEGF drug or changed to another drug under certain circumstances. Presence of activity was primarily studied on the OCT and FFA performed whenever necessary. OCT was used to detect macular oedema, subretinal fluid accumulation and pigment epithelial detachment (STRATUS and CIRRUS; Zeiss-Humphrey, Oberkochen, Germany). OCT criteria for retreatment was based on the PRONTO study. Indocyanine green angiography and autofluorescence were done whenever necessary as decided by the treating surgeon. Only eyes with poor response to anti VEGF therapy were included in this study.

Inclusion criteria included eyes primarily diagnosed as wet
ARMD and treated with anti VEGF monotherapy that lost 2 or more lines from the baseline with/ without persistence or recurrence of fluid at 1 year and were defined as poor responders. Eyes with other retinal diseases, those that had undergone laser treatment or PDT or anti VEGF therapy in the past and those eligible cases who did not have a good follow up i.e atleast 7 out of the expected 9 follow up visits after the loading dose were excluded from the study. All patients signed an informed consent for offlabel use of bevacizumab whenever used. The data was entered into a Microsoft excel sheet and statistical analysis done. Poor responders were evaluated and categorized to 4 groups- 1. mistaken diagnosis, 2. non responders, 3. tachyphylaxis, 4. complications. Those eyes which were initially diagnosed as ARMD but later identified to have variants of ARMD like PCV, RAP, Vitelliform degeneration on the basis of additional investigations like ICG, AF were grouped under “mistaken diagnosis”. Eyes that did not reveal complete resolution of the fluid on OCT/ FFA at any point of time during follow up were grouped under “non-responders”. Those eyes that showed good response to anti VEGF therapy in the form of resolution of the fluid after the loading dose and then developing recurrence of fluid with documented increase inspite of additional anti VEGF therapy were grouped under “tachyphylaxis”. Eyes that responded well to anti VEGF therapy but developed complications like RIP, macular scarring, endophthalmitis etc that led to decrease in vision formed the third group “complications”.

**Results**

Out of the 220 eyes that received anti VEGF therapy 52 eyes (23.63%) were identified as poor responders. Rest of the eyes maintained baseline vision at 1 year. The mean age of the study population was 64.67 yrs (range 52 to 80 yrs). There were 19 females (39.53%) and 29 males (60.42%). In 4 patients (8.33%) both the eyes were involved and underwent anti VEGF therapy. The mean pretreatment visual acuity was 0.6 logMAR units (range 0.1 to 1.50 logMAR units). All the patients were primarily diagnosed to have subfoveal occult choroidal neovascularisation on FFA with size of the lesion varying from 213 microns to 6420 microns GLD. Baseline OCT features included fibrovascular PED in 17 eyes, hemorrhagic PED in 6 eyes, cystoid macular edema in 16 eyes, serous PED in 18 eyes, incompletely detached hyaloid/ VMT in 11 eyes, ERM in 3 eyes, RPE bumps in 10 eyes, double layering of RPE in 4 eyes, diffuse RPE elevation in 5 eyes and scarring in 6 eyes. 30 eyes received primarily intravitreal bevacizumab and 22 eyes received intravitreal ranibizumab. 6/22 eyes that received ranibizumab converted to bevacizumab during follow up. The average number of injections received per person over 1 year of follow up was 5.43. There were 24 eyes with mistaken diagnosis, 14 eyes defined as non-responders, 11 eyes defined as tachyphylaxis. 6 eyes had complications which accounted for the decrease in vision. (Fig 1)

**Mistaken Diagnosis:** Out of the 24 eyes in this group, 19 eyes were diagnosed to have PCV, 4 eyes had RAP and 1 eye had adult vitelliform dystrophy (Table 1). 12 eyes received intravitreal ranibizumab and 12 eyes received intravitreal bevacizumab. The mean preoperative vision of this group was 0.6 log MAR and dropped to 1.05 log MAR by 1 year. The average number of injections received in this group was 4.83. The diagnosis of PCV was made on the basis of typical polyps seen on ICG angiography and prominent choroidal vasculature. These eyes initially looked like occult CNVM and had the characteristic stippled fluorescence and pooling as seen in occult ARMD. On retrospective analysis these eyes had certain characteristic OCT features at baseline including peaked PED, prominent bruchs reflectivity, hemorrhagic PED,s which were seen only in these eyes. The average number of injections received by these eyes was 5 (95/19). 7/19 eyes developed RPE rips and developed subretinal hemorrhage during follow up.

4 eyes which did not show any significant response to anti VEGF loading therapy were diagnosed to have RAP based on the typical finding of serous PED with overlying intraretinal reflectivity and hot spot on ICG angiography. At 1 year follow up all these eyes had persistent fluid/hemorrhage at the fovea, persistent PED/ CNVM was seen in 2 eyes and 1 eye showed a partial collapse of PED with retinal atrophy.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Eyes (%)</th>
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<tr>
<td>Polyoidal choroidal vasculopathy (PCV)</td>
<td>19 (79.2%)</td>
</tr>
<tr>
<td>Retinal angiomatosis proliferans (RAP)</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Adult vitelliform dystrophy</td>
<td>1 (4.2%)</td>
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1 eye which did not show any significant response to anti VEGF loading therapy was diagnosed to have adult vitelliform dystrophy based on positive autofluorescence imaging. This patient had a normal ICG and on closer scrutiny, OCT revealed increased reflective deposition in the outer segment with
areas of resorption which looked like intraretinal fluid. Over 1 year there was progressive photoreceptor IS/OS layer loss which was responsible for the vision loss. The other eye also showed increased reflectivity under the photoreceptor IS/OS layer at the level of RPE which was also positive on autofluorescence imaging.

**Nonresponders:** 14 eyes that did not show complete resolution of fluid at any point of time during follow up were identified as non responders. These eyes had persistant fluid after the loading anti VEGF therapy but majority of them had stable vision initially during follow up which later decreased over 1 year. Non responsiveness was seen in both Avastin (12 eyes) and Lucentis eyes (2 eyes). These eyes underwent ICG angiography/ AF to rule out PCV, RAP/ vitelliform dystrophy. ICG revealed indeterminate leak with prominent choroidal vasculature in 6/14 eyes. Both the patients who initially received Lucentis switched over to Avastin during follow up. The baseline OCT features in this group is shown in Table 3. The mean preoperative vision of this group was 0.9 log MAR and dropped to 1.41 log MAR by 1 year. The average number of injections received in this group was 5.64

<table>
<thead>
<tr>
<th>OCT feature</th>
<th>Eyes (%)</th>
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<tr>
<td>Multiple PED,s</td>
<td>9 (81.8%)</td>
</tr>
<tr>
<td>Bumpy RPE</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td>VMT</td>
<td>5 (45.5%)</td>
</tr>
<tr>
<td>Large Serous PED</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Reduplication of RPE</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Fibrovascular PED</td>
<td>2 (18.2%)</td>
</tr>
</tbody>
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Patients with poor response of all categories were offered combination therapy but none underwent PDT and continue to receive anti VEGF therapy.

**Complications:** No endophthalmitis, increased intraocular pressure, retinal tears or retinal detachment occurred during the observation period. 3 patients responded well to anti VEGF therapy but developed complications which lead to drop in visual acuity. 2 eyes developed RPE rips through the fovea leading to foveal degeneration and 1 patient developed macular scarring with resolution of the serous PED that he had at baseline. 3/19 eyes with PCV also developed RPE rips and developed subretinal hemorrhage with defective vision. These rips were foveolar and caused macular scarring and defective vision.

Multiple regression analysis on the predictability of the baseline OCT feature in determining poor visual outcome revealed that presense of serous PED (p 0.02), fibrovascular PED (p 0.01), diffuse RPE elevation (p 0.02), scar (p 0.04), subretinal hemorrhage (p 0.00) were associated with worsening of vision.

**Discussion**

Large-scale studies on VEGF inhibitors in neovascular ARMD have defined successful outcome as improvement in visual acuity. Thus treatment failure would include eyes that lost vision. We defined Poor responders to anti VEGF therapy as patients who lost vision by 2 lines or more compared to the baseline value. The proportion of poor responders in our study agrees with the findings in recent studies where if defined according to our criteria, approximates to 50%. Lux et al had reported that nearly 45% patients who were treated with anti VEGF were poor responders. Comparisons with published studies are difficult, as not only is case selection different but so are criteria for positive or negative change in vision. In the ranibizumab studies, the proportion of patients with deterioration or stable visual acuity is between 59- 75%. The VISION study also reported that around 40% patients treated with pegaptanib lost at least 15 letters from their pretreatment vision.

Various phase III reports on ranibizumab and pegaptanib have reported the effectiveness of VEGF antagonists independent of lesion size, lesion type and initial level of visual acuity.
Hence among the poor responders in this study, these characteristics were not studied. Baseline OCT features however may have a bearing on the outcome especially in eyes with poor response. Hence this was analysed in eyes with non-responders and tachyphylaxis.

Evidence regarding anti-angiogenesis therapy tachyphylaxis in the tumor literature is growing. Tissues treated with anti-VEGF may develop resistance to hypoxia and become less dependent on angiogenesis or develop more mature vessels through remodeling that result in stable vascularization that is less responsive to anti-angiogenic therapy. These VEGF-A-centric theories address only one side of the problem, forgetting the influence of VEGF-independent factors which may also contribute to anti-VEGF resistance. Schaal et al recently explored the concept of tachyphylaxis associated with repeat bevacizumab injections for neovascular AMD. They found that roughly 3 injections were required to decrease initial efficacy by 50%, however combining the injections with IVTA increased the number of injections to 5 before the response to therapy was less effective. A retrospective review by Forooghian et al found that it took between five and 10 injections of bevacizumab before tachyphylaxis occurred. In our study Tachyphylaxis was seen at 7-10 months after starting therapy and the mean number of injections before developing tachyphylaxis was 4.8.

CNV lesion composition may also be attributing to treatment failures. Polypoidal choroidal vasculopathy (PCV) has been suggested as a variant of neovascular AMD. Compiling results from several case series, PCV has a prevalence of 6-13% among whites and 24-50% of Asian population with neovascular AMD. In a retrospective case series, eyes deemed refractory to anti-VEGF therapy in neovascular AMD were found to have PCV and thought to be responsible to lack of treatment response. Retinal angiomatic proliferation (RAP) is another recognized lesion that responds differently than the typical CNV seen in wet AMD. Rouvas et al had reported positive results in all groups of a small prospective series comparing ranibizumab, PDT with IVTA, and PDT with ranibizumab. In our study 19 eyes were diagnosed to have PCV, 4 eyes had RAP and 1 eye had adult vitelliform dystrophy.

Another theory as to why there are non-responders is the interaction between angiopeptin and tie expressed on the surface of endothelial cells and thought to be involved in vessel stabilization through pericyte and endothelial cell interaction. This is essentially a VEGF-independent process that, in theory, could lead to aberrant angiogenesis and stabilization even in the presence of anti-VEGF antibodies. Falavarjani et al had discussed that since intravitreal antiVEGF therapy presumably does not affect the fibrous tissue, evolution of the fibrous elements may also be a reason for decreased response after repetitive injections. In our study 35.71% of eyes with non-responders had scar at baseline and could be the reason for poor outcome. VMT has been associated with an inferior visual outcome after intravitreal anti-VEGF treatment for exudative AMD. Chronic tractional forces may antagonize the effect of anti-VEGF treatment, resulting in poor response to anti-VEGF treatment with patients with VMT. In our study 45.5% of eyes with tachyphylaxis had VMT and could be the reason for poor outcome.

The question remains what to do with the non-responders. Should we consider a patient who does not improve in visual acuity after the loading dose a non-responder? For how long should we re-inject them? Further studies are needed to investigate whether patients who do not respond in visual acuity or retinal thickness after the first injection have a chance to get better with the second or third injection at all and whether there is any scope for ameliorating the result by a combination with PDT. There is some evidence to suggest that Tachyphylaxis may be partially alleviated by combining medical therapies with different mechanisms of action. The prediction of which patient will respond to antiVEGF and which will not is still not clear. Our study found that certain baseline OCT features can predict a poor visual and functional outcome. Randomised clinical trials with long-term follow-up are required to determine further reasons for poor responders.

In conclusion poor response to anti-VEGF may be due to various factors. In nearly 50% the diagnosis of AMD may be mistaken of which PCV is a major pathology. Non-responders and tachyphylaxis account for another half of cases and these eyes may require treatment modifications.

References