EDUCATIONAL HIGHLIGHTS FROM DATA PRESENTED AT THE

ANNUAL MEETING OF THE AMERICAN ACADEMY OF OPHTHALMOLOGY (AAO)

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NEW DATA CONCERNING THE USE OF ANTI-VEGF THERAPY IN THE TREATMENT OF WET AGE-RELATED MACULAR DEGENERATION

In a period of less than two years, anti-VEGF (vascular endothelial growth factor) therapies, also known as VEGF inhibitors, have emerged as the most efficacious treatment for the management of choroidal neovascularisation (CNV) secondary to age-related macular degeneration.

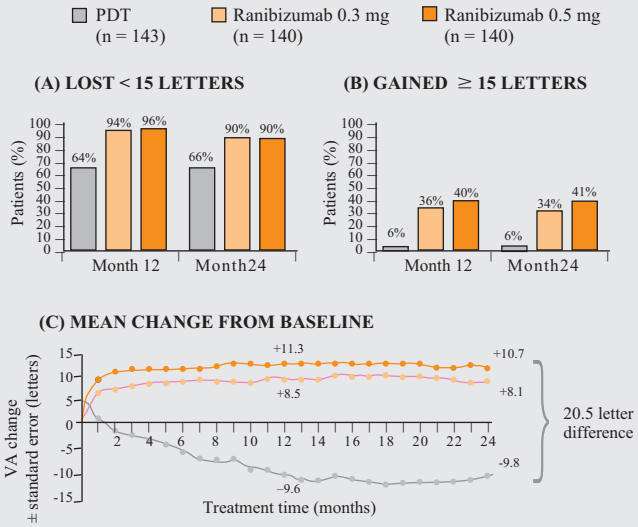
At the annual meeting of the American Academy of Ophthalmology, presenters discussed the most current data from trials with ranibizumab. Presentations included data about anatomical as well as functional changes that ranibizumab produces in the eye, and the impact of using ranibizumab in conjunction with photodynamic therapy. Attendees also learned about important differences in the how the drug is used in the European Union compared with the United States.

Reviewing the ANCHOR data

Jeffrey Heier (Department of Ophthalmology, Harvard Medical School, Boston, MA, USA) presented updated findings from the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularisation in Age-Related Macular Degeneration) study. This was one of the landmark trials with ranibizumab [1]. The trial involved three groups of patients. One group (n = 143) received verteporfin photodynamic therapy (PDT) plus sham injections of ranibizumab. The second group (n = 140) received sham PDT treatments plus intravitreal injections of ranibizumab 0.3 mg. The third group (also n = 140) differed from the second only in that the injected doses were 0.5 mg.

At both 12 and 24 months follow-up, patients who were treated with 0.5 mg ranibizumab had significantly better responses in visual acuity (VA) as measured by ETDRS (Early Treatment of Diabetic Retinopathy Study) letter scores, than patients treated with verteporfin PDT (Figure 1). Unlike PDT, which only slows the progress of neovascular growth, treatment with ranibizumab actually reverses the progress of the disease. At 24 months follow-up, there was a difference of ≥20 ETDRS letters between patients who were treated with 0.5 mg ranibizumab and those who received PDT. In this study, fully 40% of the patients treated with ranibizumab made improvements in VA. Most of this success was achieved in the group which received the 0.5 mg dose.

Figure 1 ANCHOR: KEY VISUAL ACUITY END POINTS



VA = visual acuity
Last observation carried forward approach was used for missing data

Source: Heier J. Data presented at the Annual Meeting of the American Academy of Ophthalmology (AAO). New Orleans, LA, USA, 2007.

No major safety concerns

Dr. Heier's latest data covered safety findings over two years, and he reported that there were few significant differences in safety concerns between ranibizumab and PDT. More cases of

systemic hypertension were seen among patients treated with verteporfin PDT (16.1%) compared with ranibizumab 0.5 mg (12.1%). However, non-ocular haemorrhage occurred in more patients treated with ranibizumab (9.3%) compared with the verteporfin PDT (4.9%). Cardiovascular adverse events were not markedly different between the arms; mortality from vascular causes, nonfatal myocardial infarction and nonfatal cerebrovascular accidents occurred in 4.2% of patients treated with PDT compared with 5.0% of patients treated with ranibizumab. Presumed endophthalmitis occurred in 1.1% and serious uveitis occurred in 0.4% of ranibizumab-treated patients. There were no cases of either adverse effect among PDT-treated patients.

Anatomical responses

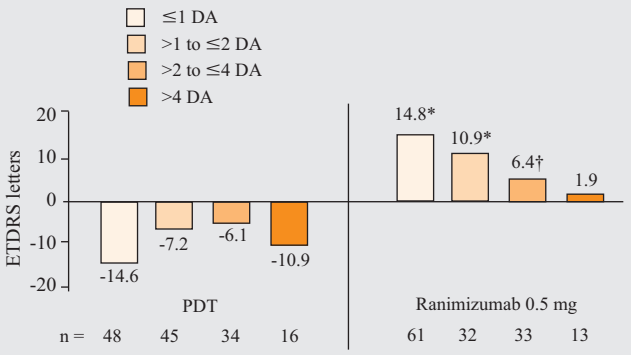
Dr. Heier said it is important to know that ranibizumab produces measurable anatomical improvements, and that these anatomical responses are associated with functional improvements. For example, the mean change in the CNV lesion area, as measured by Disc Area (DA), increased fivefold more among patients treated with verteporfin PDT, compared with patients who received either dose of ranibizumab. Conversely, the area of the lesion that was leaking blood, as seen on fluorescein angiography, was reduced by approximately threefold more in the ranibizumab-treated patients compared with the PDT-treated patients. It was this reduction in neovascular leakage, along with regression of existing subretinal-pigment epithelium oedema, that led to the improvements in VA, Dr. Heier said.

Subgroup analysis

Subgroup analyses showed that the improvements with ranibizumab were seen in patients across a spectrum of ages, degrees of visual acuity, and lesion size, whereas the changes with PDT were confined to smaller subsets of patients. For example, significantly more patients treated with ranibizumab lost <15 letters compared with PDT-treated patients overall. For patients whose baseline VA was 20/63 or better, the mean change at 24 months was an improvement of 5.3 letters for ranibizumab-treated patients, versus a *loss* of 16.7 letters in the PDT-treated patients. Patients whose baseline VA was between 20/80 and 20/100 had a mean increase of 11.6 letters when treated with ranibizumab, compared with a decrease of 13.9 letters when treated with verteporfin PDT.

The size of the CNV lesion at baseline also predicted outcome. The best improvements in vision, defined as a gain of ≥15 letters, were observed among 54% of ranibizumab-treated patients whose baseline lesions were ≤1 DA. By contrast, only 4% of patients who were treated with PDT and whose baseline lesions were ≤1 DA had a 15-letter increase. Overall, patients treated with ranibizumab had mean improvements in VA ranging from 1.9 letters for those whose lesion size was >4 DA, to 14.8 letters for those whose lesion size was ≤1 DA (Figure 2). In contrast, no patients treated with PDT had mean improvements in letter scores at 24 months for any lesion size. And yet the VIP trial in 2001 reported that PDT had the greatest treatment benefit among patients whose lesions were <4 DA [2].

Figure 2 **MEAN CHANGE IN VA AT MONTH 24 BY CNV LESION AREA AT BASELINE**



* p < 0.0001 vs. PDT
† p < 0.005 vs. PDT

VA = visual acuity; CNV = choroidal neovasularisation; ETDRS = Early Treatment of Diabetic Retinopathy Study; PDT = photodynamic therapy

Source: Heier JS. Data presented at the Annual Meeting of the American Academy of Ophthalmology (AAO). New Orleans, LA, USA, 2007.

Dr. Heier concluded that these are important findings since they show that ranibizumab is effective across a large range of lesion sizes and baseline visual-acuity scores. Also, at 24 months, all key anatomical outcomes based on fluorescein angiography favoured ranibizumab over verteporfin PDT.

Using a different dosing schedule

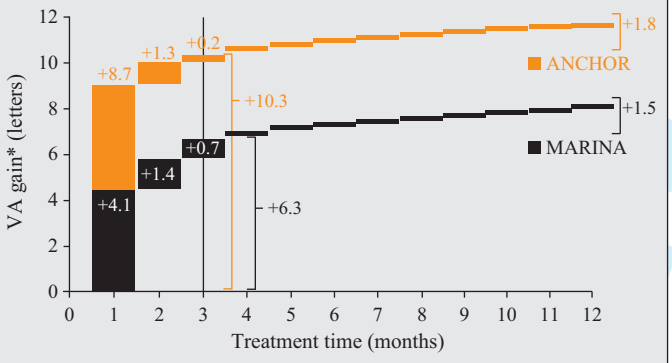
An issue that concerns many clinicians is how often, or for how long, anti-VEGF therapies should be used. It is known, for example, that VEGF inhibitors have a short half-life, so their effects wear off fairly quickly. Regular injections of ranibizumab could be needed indefinitely. Even though the high cost of ranibizumab is paid by insurers in many EU countries, this expense cannot be ignored by insurance companies or national healthcare payers. Will any improvements seen in visual acuity be sustained over time, or will regular monthly injections be needed?

According to Ursula M. Schmidt-Erfurth (Department of Ophthalmology, Medical University of Vienna, Vienna, Austria), most of ranibizumab's benefit occurs within the first three months of treatment. The improvements in VA between months 3 and 12 reported in the ANCHOR study and in another landmark study, the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration) trial [3], were quite modest — 1.8 and 1.5 letters for the two studies, respectively (Figure 3). Therefore, Prof. Schmidt-Erfurth reasoned that it could be feasible to stop

ranibizumab treatment once the maximum individual treatment response has been achieved. This hypothesis was tested in two small trials, which ultimately helped answer the question of whether monthly treatment with ranibizumab must be maintained.

Figure 3 **MAJORITY VA GAIN OCCURS WITHIN THE FIRST THREE MONTHS OF RANIBIZUMAB TREATMENT**

Duration of loading phase of three months: justified by mean change of VA between visits



* Ranibizumab 0.5 mg
VA = visual acuity

Source: Schmidt-Erfurth UM. Data presented at the Annual Meeting of the American Academy of Ophthalmology (AAO). New Orleans, LA, USA, 2007.

One of these trials [4] demonstrated that clinically important improvements in VA (mean 9.3 letters; $p < 0.001$) as well as meaningful reductions in retinal thickness (mean 178 µm; $p < 0.001$) could be achieved when patients were given a loading dose of three monthly injections. Subsequent injections were given only when VA deteriorated, or when there was an increase in retinal thickness (as measured with optical coherence tomography), or when there was other evidence that the patient was a nonresponder.

European versus American treatment scheduling

The results of the trials were largely similar, but they have been interpreted somewhat differently by regulatory authorities in the European Union and in the United States. In the US, ranibizumab is indicated primarily as a monthly treatment. If ongoing monthly treatments are not feasible, then dosing every three months, following an initial course of four monthly injections, may be an option. VA monitoring would be needed indefinitely, and treatment should be re-initiated if the patient loses ≥5 letters between treatments.

In the EU, ranibizumab is given in three initial monthly injections, and further treatments are given *only* if the patient shows a loss in VA of >5 letters. Monthly monitoring, including testing for VA and retinal thickness, is mandatory. This demonstrates a subtle, but important difference in the accepted timing of ranibizumab treatments in Europe versus America.

Regardless of what treatment algorithm is chosen, the optimal regimen must be individualised for every patient, and retreatments must be based on functional as well as anatomical measures, Prof. Schmidt-Erfurth concluded. She said that consideration must be given to offering each patient the best treatment possible, with the least disruption to the patient's quality of life.

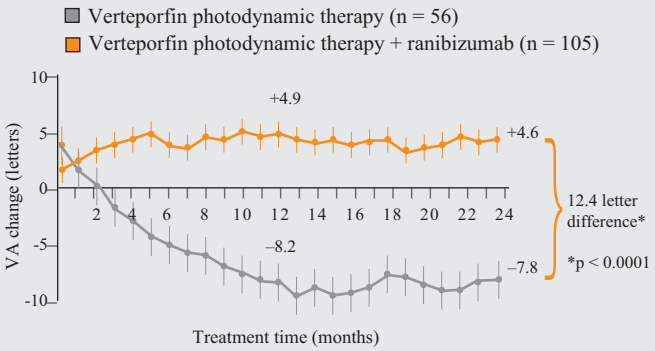
Combination therapy

It is interesting to note that despite the improvements seen with ranibizumab alone, it remains a common practice to use this drug in combination with verteporfin PDT, which used to be the gold standard for treating macular degeneration. Ongoing studies are currently evaluating the use of this therapeutic combination under various delivery protocols.

Paolo Lanzetta (Department of Ophthalomology, University of Udine, Udine, Italy) discussed updated findings from the FOCUS (RhuFab V2 Ocular Treatment Combining the Use of Visudyne® to Evaluate Safety) study, in which patients were treated with either verteporfin PDT and a sham injection of ranibizumab (n = 56), or with ranibizumab 0.5 mg and verteporfin PDT (n = 106) [5]. All of these patients had predominantly classic subfoveal wet AMD, and received the PDT at baseline, followed by ranibizumab or the sham injection seven days later. Ranibizumab or the sham injection was also given at monthly intervals for the following 23 months, and PDT was delivered at three month intervals, if needed.

The initial findings showed that at 12 months follow-up, 90% of patients who received the combination therapy maintained or improved VA (mean *increase* of 4.9 letters). In comparison, 68% of those who received PDT alone had a mean *decrease* of 8.2 letters. These results were similar at 24 months follow-up ($p < 0.0001$; Figure 4).

Figure 4 **FOCUS: MEAN CHANGE IN VA OVER TIME**



VA = visual acuity

Source: Heier JS, et al. Arch Ophthalmol 2006;124:1532–1542; Lanzetti P. Data presented at the Annual Meeting of the American Academy of Ophthalmology (AAO). New Orleans, LA, USA, 2007.

At the end of the first year, there were more cases of uveitis and transient inflammation among patients who received ranibizumab. This was felt to be related to the lyophilised formulation of the drug, and a protocol mandate was ordered so patients in the following year received the commercially available liquid formulation of ranibizumab instead.

There was a marked reduction in the number of new cases of inflammation in the following year when the liquid formulation of ranibizumab was used. Nonetheless, investigators have hypothesised that some of the inflammation might be caused by the time delay between administering the PDT and adding ranibizumab. At least three trials are now being conducted to examine the role that same-day delivery of the treatments may produce.

Overall, the updated information from the FOCUS study has shown that combining ranibizumab with verteporfin PDT is effective out to at least two years follow-up. It also appears that combination therapy with the two agents may reduce the number of treatments that are needed.

Conclusion

Current practices with respect to ranibizumab indicate that the drug does not need to be used on a regular monthly basis, and that alternative dosing regimens are feasible, provided that patients are monitored for signs of VA deterioration or anatomical change. Nor does ranibizumab need to be administered concomitantly with verteporfin PDT; it works well on its own. However, if it is used as adjunctive therapy, there may be a synergistic effect that reduces both the overall number of injections of ranibizumab as well as the number of PDT treatments required. It also appears that same-day delivery of the two therapies may help reduce the risk of uveitis and ocular inflammation.

In any case, ranibizumab is still the only approved treatment for age-related macular degeneration shown to actually improve visual acuity and restore lost vision, rather than merely arrest the progress of the disease.

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