9:56 AM

Response to Treat-and-Extend Therapy in Wet AMD Patients Shows Differentially Expressed Proteins Specific to CNV Signaling Pathways Shed Into the Vitreous

- Bert M. Glaser, MD
- Stephanie M Ecker, MS
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OBJECTIVE To investigate differentially expressed protein signaling pathways of responders versus non-responders, during their “Treat and Extend” protocol of anti-VEGF treatment.

PURPOSE In the past decade, the use of anti-VEGF treatments has revolutionized the treatment for wet AMD, but there is no set treatment regimen that is successful in all patients. Herein, patients under one of the common treatment protocols termed “Treat and Extend” therapy (TER) are studied to discover the vitreous biomarker differences in those who experience vision stability versus vision loss.

METHODS A total of 42 vitreous aspirates were taken before and after 21 TER extended treatment follow-up intervals. The patients were split into two groups, depending on how their visual acuity was affected by the extended follow-up interval. Patients were considered minimally affected if their VA decreased by less than 10 letters on the

ETDRS chart; if VA decreased by more than 10 letters, they were considered to have progressive loss of vision. Each vitreous aspirate was probed against 37 proteins whose functionality (such as: angiogenesis, inflammation, hypoxia) has direct correlation to wAMD. This was performed using RPPM (reverse phase protein microarray) technology.

RESULTS Patients who had VA that was minimally affected during the extended follow-up interval had a significant increase in expression levels of 8 proteins that point to an increase in AKT/PI3K regulation of nitric oxide. The proteins include AKT T308 (P= 0.0322), eNOS S1177 (P= 0.0288), PDGFRβ Y716 (P= 0.0210) and VEGFR2 Y996 (P= 0.0425). A protein-protein interaction pathway analysis confirmed this finding. In the patients who had progressive vision loss, no proteins that had a significant change in expression level. A protein-protein interaction pathway analysis was done, and suggests that the patients with progressive vision loss are being affected by oxidative stress induced activation of MAPK signaling pathway.

CONCLUSION When Bevacizumab treatment is suspended due to an extended treatment follow-up interval, 8 proteins significantly increase. However in the patients with VA progression, the same 8 proteins have no change in expression level during the extended follow-up interval. This suggests that anti-VEGF treatment has a depressing effect upon these protein networks before suspension.

TAKE HOME MESSAGE Patients classified as “responders” to anti-VEGF treatments express significantly different protein levels in their vitreous humor than those “non-responders”.

10:04 AM

Visual Acuity Response as a Function of the Affinity and Vitreous Half-Life of Intravitreally Administered Anti-VEGF Agents

- Robert L. Avery, MD
- Kha Le, PhD
- Tong Lu, PhD
- Gary Sternberg, MD, MBA
- Jennifer E Visich, PhD

OBJECTIVE To predict visual acuity (VA) gain as a function of affinity and intravitreal half-life of Vascular Endothelial Growth Factor A (VEGF) inhibitors in AMD patients.

PURPOSE Ranibizumab and aflibercept both bind VEGF with high-affinity and inhibit its function in vitro and in vivo. There are suggestions that aflibercept has higher binding affinity, though in vitro and clinical data suggest that the molecules are equipotent and have comparable clinical efficacy. We described the relationship between VEGF-binding affinity, intravitreal (ITV) half-life ($\tau_{1/2}$) and VA.

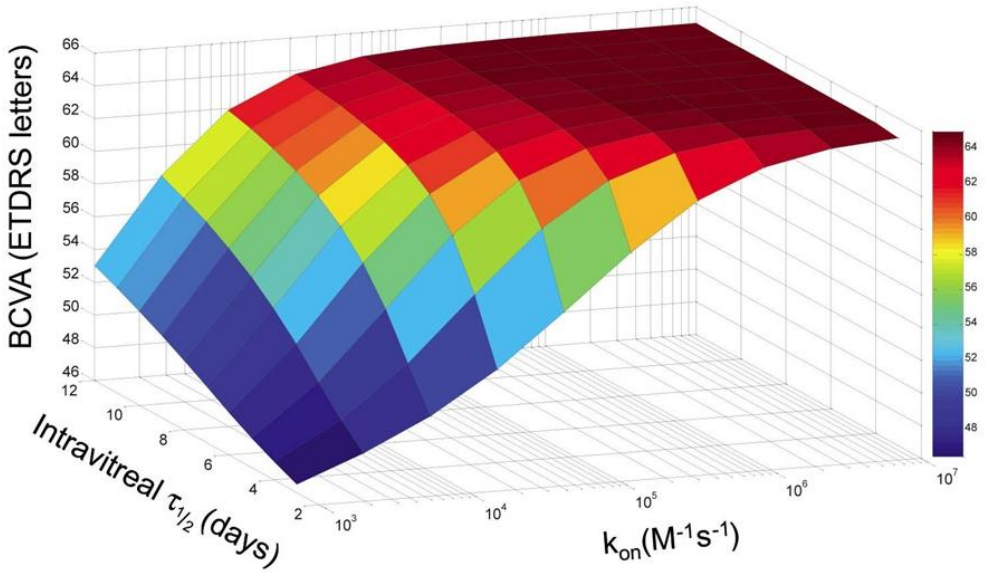
METHODS A semi-mechanistic pharmacokinetic-pharmacodynamic (PK/PD) mathematical model was developed to predict clinical VA response in patients with age-related macular degeneration (AMD) as a function of affinity, specifically the association constant (k_{on}), of VEGF inhibitors and their intravitreal $\tau_{1/2}$. The model takes into account AMD disease progression as related to VEGF levels, target mediated drug disposition, and a VEGF-VA relationship. Simulations were performed to test the importance of changes in these parameters in relation to VA. Best Corrected Visual Acuity (BCVA) data as well as the PK data from the ranibizumab Phase 3 trial MARINA (n= 716 patients) were used for model validation.

RESULTS The model predictions for monthly dosing demonstrate that regardless of major changes in the k_{on} and intravitreal $Ï„_{1/2}$ (in ranges that include published values for ranibizumab and aflibercept) these high-affinity VEGF inhibitor molecules lay squarely on the maximal VA benefit plateau (Figure). This is confirmed by clinical evidence, which suggests that both ranibizumab and aflibercept lead to similar benefits in VA outcomes. These observations will be further validated with comparative $Ï„_{1/2}$ data from *in vivo* cynomolgus monkeys and *in vitro* binding affinity studies. The cynomolgus monkey study evaluated the pharmacokinetics and disposition of 0.5 mg ranibizumab and 2.0 mg aflibercept following intravitreal injection (10 animals per drug) and intravenous infusion (4 animals per drug).

CONCLUSION Using clinical trial results, a PK/PD model relating the PK of anti-VEGF molecules and VA, demonstrates that once reaching a k_{on} of approximately $>10^5$ $M^{-1}s^{-1}$, further affinity improvement does not translate to increased efficacy in this model. Other factors, such as potency, are expected to impact the overall clinical efficacy of high-affinity VEGF inhibitors such as ranibizumab and aflibercept.

TAKE HOME MESSAGE

A PK/PD mathematical model of anti-VEGF Fab and soluble decoy receptor molecules suggests that there is a threshold beyond which further affinity improvement does not translate into greater VA gain.



10:12 AM

Intraocular Pressure in Patients with Neovascular AMD Receiving Intravitreal Aflibercept Injection or Ranibizumab

- K. Bailey Freund, MD

OBJECTIVE This analysis of the VIEW 1 and VIEW 2 studies will provide an understanding of the change in intraocular pressure in wet AMD patients treated with intravitreal aflibercept injection or ranibizumab.

PURPOSE To evaluate change in intraocular pressure (IOP) in patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) receiving intravitreal aflibercept injection (IAI; also referred to as VEGF Trap-Eye) or ranibizumab in two, randomized, Phase 3 clinical studies (VIEW1, VIEW2).

METHODS A total of 2457 patients with AMD were randomized to four treatment groups: IAI 2 mg every 4 weeks (2q4), 0.5 mg every 4 weeks (0.5q4), 2 mg every 8 weeks (2q8, after three initial monthly doses), or ranibizumab 0.5 mg every 4 weeks (Rq4). In this analysis, incidence of changes in IOP >10 mm Hg from baseline and proportion of patients with IOP >21 mm Hg were analyzed. In addition, Kaplan-Meier methodology was employed to evaluate sustained (2 consecutive months) incidences of IOP >21 mm Hg.

RESULTS All treatment groups were equally balanced at baseline with respect to IOP measures. Proportions of patients at Week 52 in the Rq4, 0.5q4, 2q4, and 2q8 groups with an increase of>10 mm Hg in IOP from baseline were 3.2%, 2.3%, 1.1%, and 2.3%, respectively. At Week 52, the corresponding proportions of patients with an IOP >21 mm Hg were 13.6%, 8.2%, 10.1%, and 8.0%. A similar trend was seen in the fellow eyes. Compared with Rq4, the IAI groups had a significantly lower incidence of sustained IOP > 21 mm Hg by 52% (95% CI: 12%, 75%), 70% (CI: 40%, 87%), and 54% (CI: 15%, 76%) for the 2q4, 0.5q4, and 2q8 regimens, respectively, during the 52 weeks of treatment. The proportions of patients initiating IOP-lowering interventions were low in all groups. These data are consistent through the second year of the studies.

CONCLUSION During the first year of the VIEW studies, the incidence of IOP increase was low and similar among the IAI groups and lower than was seen with ranibizumab.

TAKE HOME MESSAGE During the first year of the VIEW studies, the incidence of IOP increase was low and similar among the IAI groups and lower than was seen with ranibizumab.

10:26 AM

Autologous Transplantation of RPE and Choroid for the Treatment of Wet AMD: Functional Results and Prognostic Factors after a Long-Term Follow Up

- Barbara Parolini, MD
- Grazia Pertile

OBJECTIVE Autologous transplantation of RPE and choroids may be an alternative treatment for specific types of wet AMD. The prognostic factors may guide case selection.

PURPOSE Cases of wet age related macular degeneration (AMD), which do not respond to standard care, may be treated with autologous transplantation of retinal pigment epithelium (RPE) and choroid (patch). The purpose of the study was to find out the prognostic factors, in order to increase the functional and anatomical success of this surgical intervention.

METHODS Forty eyes with a choroidalnevascularization (CNV) due to AMD underwent vitrectomy, CNV removal and a patch. Each eye was tested with ETDRS preoperatively and 1 week, 2 weeks, 1 month and than 6,12,24 and 36 months postoperatively. At the same visits, the patients received an OCT scan and a fluorescein and indocianine green

angiography (Heidelberg). The following parameters were evaluated preoperatively: the visibility of the inner and outer segment junction (IS-OS) and of the external limiting membrane (ELM). The following parameters were evaluated postoperatively: the visibility of IS-OS, the central foveal thickness (CFT), the thickness of the patch, the revascularization of the patch.

RESULTS Preoperatively 8 eyes had BCVA ≤ 1. At three years follow up, 10 eyes had BCVA ≤ 1. The average preop and postop BCVA was 1.7 and 1.4 logMar respectively. Thirty-four patches were revascularized by two weeks postoperatively. The central foveal thickness and the thickness of the patch normalized by 1 month. The IS-OS segment layer became visible in one month. Visibility of the IS-OS at the preop OCT was correlated with stabilized or improved BCVA postoperatively.

CONCLUSION Preoperative visibility of the IS-OS at the OCT was the major prognostic factor.

TAKE HOME MESSAGE Autologous transplantation of RPE and choroids may be an alternative treatment for specific types of wet AMD. The prognostic factors may guide case selection.

10:34 AM

Patient Perceptions of the Treatment Regimen and Expected Outcomes of Intravitreal Anti-VEGF Injections for Wet Age-Related Macular Degeneration

- Tarek S. Hassan, MD
- Caesar K. Luo, MD
- George A. Williams, MD

OBJECTIVE To present the results of a large survey of patients, who received multiple intravitreal anti-VEGF injections for wet AMD, that describes their opinions of their disease and their treatment course.

PURPOSE A regimen of multiple repeated intravitreal injections of anti-VEGF agents is the standard of care treatment for wet age-related macular degeneration (AMD). This approach requires frequent examinations, testing, and injections. We report the results of the first large-scale survey to evaluate patient attitudes and opinions towards their disease course and extensive treatment experiences.

METHODS 150 consecutive patients, actively being treated with bevacizumab or ranibizumab for wet AMD, completed a 15-question survey that assessed their opinions about various treatment related issues including: Willingness to indefinitely continue injections, factors impacting drug choice, value of new drugs and surgery to lessen injection frequency, treatment of bilateral disease, expected disease outcomes, and concern over costs and insurance coverage of drugs, testing, and procedures. All questions were fully explained and patients had ample time to complete the survey at a single sitting. Answers were tabulated and correlated with the drug used and numerous treatment and patient variables.

RESULTS 96 women, 54 men completed the survey. A mean of 11.8 injections (either drug) were given over a mean of 31 months. *Most pts*: Are very willing [1-5 scale, 5 = highest] to continue indefinite monthly injections to improve VA (4.875) or maintain VA (4.75), would agree to lifetime monthly injections (87%), expect VA improvement (50%) [28% expect a cure], prefer monthly exams with prn injections (71%) vs. planned monthly injections, consider good outcomes (73%) over all other features (cost, FDA approval, complication rates) in choosing a drug, prefer a more expensive FDA-approved drug (69%) vs. others, would switch to a less frequently injected drug regardless of outcomes with other drugs (57%) or despite good outcomes with other drugs (31%), would consider surgery only if they could achieve better VA than with injections (57%). Most dislike post-injection antibiotic drops > redness > testing > pain > cost > frequent visits > transportation issues. Drug choice had no impact on results.

CONCLUSION This report is the first to describe the attitudes and opinions of wet AMD patients towards numerous aspects of their treatment regimen of repeated intravitreal anti-VEGF injections. Expanding drug and protocol options make it increasingly important to understand how wet AMD patients view their treatments. VA outcome is an important factor, and drug choice is not, in shaping their impressions.

TAKE HOME MESSAGE Most wet AMD patients are very willing to undergo the intensive regimen of repeated intravitreal anti-VEGF injections, and view these experiences very positively, especially if VA outcomes are good.

10:42 AM

PEARL2: High-Dose 2 mg Ranibizumab, Continuous Monthly Treatment, for Polypoidal Choroidal Vasculopathy (PCV) – 6 Month Results

- Gregg T. Kokame, MD, MMM
- James C. Lai, MD
- Raymond Wee, MD

OBJECTIVE To report the 6-month results from the PEARL2 trial which is evaluating the efficacy and safety of monthly intravitreal injections of 2.0mg ranibizumab in patients with active PCV

PURPOSE Primary outcomes are stabilization of vision (loss of <15 ETDRS letters) and incidence of ocular and systemic adverse events. Secondary outcome measure are changes in visual acuity, subretinal or sub-retinal pigmented epithelial hemorrhage, retinal pigmented epithelial detachments, central foveal thickness (CFT), fluorescein leakage, polypoidal polyps and complexes.

METHODS Prospective, open-label, investigator-sponsored trial of monthly intravitreal ranibizumab (2.0mg) for PCV. Patients enrolled have active PCV, defined as exudation or bleeding as a result from the polypoidal complexes and polyps. Patients enrolled were either treatment-naive or had prior anti-VEGF therapy. Patients with prior PDT were excluded from this study. The first 6 month results from the 14 of 24 patient are included in this report.

RESULTS 14 patients (14 eyes) finished the 6-month treatment. No significant adverse events were noted. No patient lost ≥15 letters. At 6 months, patients receiving 2.0mg ranibizumab for PCV showed a 14% chance of gaining ≥15 letters and a 86% chance of stable vision. Retinal or subretinal pigmented epithelial hemorrhage resolved or

decrease in 8 of 8 eyes (100%) at 6 months. RPEDS resolved or decreased in 8 of 11 eyes (73%). RPEDS remained unchanged in 3 of 11 eyes (27%). Subretinal fluid resolved or decreased in 11 of 14 eyes (79%). Subretinal fluid remained unchanged in 2 of 14 eyes (15%). Subretinal fluid resolved and then recurred in 1 of 14 eyes (7%). CFT decreased from 298 μm at baseline to 208 μm on average in the 14 of 14 eyes. In 11 of 14 eyes with significant macular edema (<275 μm), the CFT decreased from 310 μm at baseline to 208 μm. The polypoidal complexes decreased in 8 of 14 eyes (57%) and remained stable in 6 of 14 eyes (43%).

CONCLUSION Continuous 2.0mg ranibizumab is safe and well-tolerated in eyes with PCV. Preliminary results show stabilization of vision similar to those eyes in PEARL, resolution of subretinal hemorrhage, decrease of macular edema. The higher dose of medication showed positive improved regression of RPED and polyps.

TAKE HOME MESSAGE Discuss the effects of anti-VEGF on active polypoidal choroidal vasculopathy