Purpose: Previously we demonstrated that targeted Arg-Gly-Asp (RGD) intraceptor Flt23k nanoparticle (RGD.Fltn23k.NP) inhibits choroidal neovascularization (CNV) in murine and monkey models. The present study measures the dose response and efficacy of intravenously administered RGD.Fltn23k.NP on regression of laser-induced CNV in mice to establish its safety and tolerability.

Methods: To determine whether RGD.Fltn23k.NP nanoparticles exhibit dose dependent inhibition and regression of laser-induced CNV, Anesthetized, 6-8 week old male C57Bl/6J mice received laser injury in both eyes. One week after laser injury, mice were treated with 0 (PBS), 1, 3, 10, 20, 30, or 40µg RGD.Fltn23k.NP suspension via tail vein (n = 7 mice). CNV size was assessed by fluorescein angiography (FA) and optical coherence tomography (OCT) at baseline (post laser 1 week) and 2 weeks after treatment. To assess safety and tolerability of the Fltn23k nanoparticles, we intravenously injected 5 male and 5 female mice with a single treatment of RGD.Fltn23k.NP. Based on the above dose-efficacy assay. Systemic toxicity was evaluated after one month by assaying hematology, histology, immune responses, and changes in mortality and body weight. The control groups included untreated C57Bl/6J and C57Bl/6J mice receiving an identical dose of RGD delivery blank nanoparticles (RGD.Bk.NP).

Results: Compared to CNV volumes 1 week post laser (baseline) v, the CNV volumes evaluated at 2 weeks were decreased by 4.19%, 9.43%, 9.61%, 22.52%, 27.18%, 29.70%, and 39.81%, corresponding to: PBS, 1, 3, 10, 20, 30, and 40 µg of plasmid respectively. We choose a plasmid dose of 30 µg to evaluate safety in mice. The treated mice showed equivalent mortality to controls, while body weights were not statistically different. The concentration of hemoglobin in red blood cells was 2.59 ± 0.27 g/dl, 2.62 ± 0.34 g/dl, and 2.60 ± 0.21 g/dl in the wildtype, RGD.Bk.NP, and RGD.Fltn23k.NP groups respectively. The concentration of complement C3 in plasma was 581.45 ± 82.07 µg/ml, 633.13 ± 95.82 µg/ml, and 614.60 ± 102.05 µg/ml in wildtype, RGD.Bk.NP, and RGD.Fltn23k.NP groups respectively. Both the concentrations of hemoglobin and complement C3 were not statistically different between RGD.Fltn23k.NP and control groups.

Conclusions: Intraceptor Fltn23k nanoparticles dose-dependently improve recovery from CNV injury and are well tolerated with no obvious systemic defects.

Commercial Relationships: Xiaohui Zhang; Austin Bohner, None; Sailaja Bondalapati, None; Santosh K. Kumar Muddana, None; Hironori Uehara, None; Bonnie Archer, None; Balamurali Ambati, None

Support: NEI 5R01EY017182

Program Number: 3323 Poster Board Number: D0126
Presentation Time: 8:30 AM–10:15 AM
Systemic VEGF Inhibition does not modulate ocular inflammatory cell infiltrate in the murine laser-induced choroidal neovascularization (CNV) Model
Adrian Will-Orrego, Sha-Mei Liao, Yubin Qiu, Elizabeth Fassbender, Siyuan Shen, Namrata Kotagiri, Bruce D. Jaffe, Stephen H. Poor.
Ophthalmology, Novartis Institutes for Biomedical Research, Cambridge, MA.

Purpose: To investigate ocular inflammatory cell infiltration in a murine laser-induced CNV model.

Methods: Laser pulses were applied to mice eyes and CNV area measured by i.v. injection of a vascular label, RPE-choroid flat mount imaging, and quantification of CNV area by morphometric analysis. CNV area and cellular infiltrate were assessed 7 days after laser application in mice systemically administered an anti-VEGF Ab

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(“4G3”) or saline. To study cellular infiltration, labeled antibodies were used to identify microglia (Iba-1+) and macrophages (F4/80+). Images of the ocular flat mounts were captured using AxioVision software (Zeiss). Iba-1+ microglia cells peripheral to the CNV lesion were randomized and counted semi-automatically using Matlab, and the F4/80+ macrophages were counted manually. CNV area and cellular infiltrate were analyzed in sex matched Chemokine (C-C Motif) Ligand 2 (CCL2) knockout (KO) and wild-type (WT) littermate controls.

Results: 7 days after laser ocular flat mounts demonstrated microglia cell populations were increased by 61% (N = 16 - 20 eyes per group, p = 0.007) and no changes were seen in retinal macrophages (n = 5 retinas per group, p = 0.36) compared to non-lasered mice. Mice administered an anti-VEGF Ab demonstrated an average of 46% reduction in CNV area (p = < 0.0001), but no difference in subretinal microglia compared to vehicle treated mice (n = 2 Studies, n ≥ 10 eyes/group, p ≥ 0.22). CNV area was increased in CCL2 KO compared to WT controls (n = 2 studies per sex, males average increase CNV area = 67.8%, females 48.1%, n = 9 - 15 mice per group, p ≤ 0.007 in 3 studies, p > 0.05 in one study). CCL2KO mice had similar numbers of subretinal microglia and retinal macrophages compared to WT mice (n = 10 eyes/group p = 0.23).

Conclusions: Anti-VEGF therapy reduces CNV area, but has no effect on microglia and macrophage infiltrate. CCL2 genetic KO increases CNV area, but shows no alteration in cellular infiltrate numbers. Functional changes in cellular infiltrate rather than number may play a key role in ocular angiogenesis.

Commercial Relationships: Adrian Will-Orrego, Novartis Institutes for Biomedical Research; Sha-Mei Liao, Novartis Institutes for Biomedical Research; Yubin Qiu, Novartis Institutes for Biomedical Research; Elizabeth Fassbender, Novartis Institutes for Biomedical Research; Siyuan Shen, Novartis Institutes for Biomedical Research; Namrata Kotagiri, Novartis Institutes for Biomedical Research; Bruce D. Jaffee, Novartis Institutes for Biomedical Research; Stephen H. Poor, Novartis Institutes for Biomedical Research

Program Number: 3324 Poster Board Number: D0127

Presentation Time: 8:30 AM–10:15 AM

Retinal Toxicity of Intravitreal Injection of Ziv-Aflibercept in albino rabbits

Dan M. Ramon1, Yonathan Shahar1, Amir Massarweh1, Irit Mann1, Ido Perlman1, Anat Loewenstein1,2

1Department of Physiology and Biophysics, Technion-Israel Institute of Technology, Ruth & Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; 2Department of Ophthalmology, Tel-Aviv University, Tel-Aviv, Israel; 3Department of Physiology and Biophysics, Technion-Israel Institute of Technology, Ruth & Bruce Rappaport Faculty of Medicine, Haifa, Israel

Purpose: Ziv-aflibercept (Zaltox, Sanofi-aventis U.S. LLC, Bridgewater, NJ), a drug indicated for patients with colon cancer, acts as a soluble receptor that binds to human Vascular Endothelial Growth Factors 1 and 2, and to human Placental Growth Factor. Aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) the Intravitreal equivalent of ziv-aflibercept, is an FDA approved drug for the treatment of neovascularization in age-related macular degeneration, of macular edema following retinal vein occlusion and of diabetic macular edema. The aim of this study is to evaluate retinal toxicity of ziv-aflibercept.

Methods: A total of 18 albino rabbits were injected intravitreally with 0.1 ml of ziv-aflibercept solution into the experimental eye and 0.1 ml saline into the control eye. Twelve were used for electroretinogram (ERG) 4-weeks follow-up (one of these died) and 6 were used for histological and glial fibrillary acidic protein (GFAP) immunocytochemistry during follow-up. ERG responses were recorded 3 days, 1-, 2-, and 4-weeks after injection. The visual evoked potential (VEP) was recorded after 4 weeks. Immunohistochemical and histological studies were performed throughout the follow-up period and after the termination of the follow-up period.

Results: the ERG responses of the experimental eyes did not show any significant difference from the responses of the control eyes, either in amplitude or in pattern, throughout the follow-up period. The flash VEP responses of the experimental eyes were of normal pattern and amplitude and were similar to those recorded by stimulation of the control eyes. Histologic studies of both experimental and control eyes did not show any signs of structural damage. However, GFAP immunocytochemistry showed activation of retinal Müller cells, indicating mild retinal gliosis.

Conclusions: Ziv-aflibercept was found to be non-toxic to the retina of rabbits based on electrophysiological testing and histologic examination. However, GFAP immunocytochemistry suggests mild retinal stress caused by the drug. Therefore, application of intravitreal ziv-aflibercept in patients needs caution and additional considerations.

Commercial Relationships: Dan M. Ramon; Yonathan Shahar, None; Amir Massarweh, None; Irit Mann, None; Ido Perlman, None; Anat Loewenstein, None

Program Number: 3325 Poster Board Number: D0128

Presentation Time: 8:30 AM–10:15 AM

Ranibizumab and Bevacizumab treatment after retinal ischemia-reperfusion injury in a rodent model

Marina Romer, Stephanie Lohmann, Dustin Schulte, Gesa Stute, H Burkhard Dick, Stephanie C. Joachim. Experimental Eye Research Institute, University Eye Hospital, Bochum, Germany.

Purpose: Ischemia-reperfusion (I/R) results in functional and morphological damage of different retinal cell types. The aim of this study was to investigate the effects of intravitreal ranibizumab and bevacizumab treatment, VEGF inhibitors, on retinal cells after ischemic injury.

Methods: I/R was induced by raising the IOP to 140 mmHg for 1h in one eye of rats (n=5-6/group). One day after I/R the VEGF inhibitors were intravitreally injected. The untreated eye served as control (Co). 14 days after ischemia ERG measurements were performed. Retinal ganglion cells (Brn-3a), microglia (Iba1) as well as activated microglia (ED1) were stained on retinal cross-sections. Additionally, apoptosis (Bax) and the early (LC3BII) and late (LAMP1) autophagocytosis were analyzed using immunohistochemistry. Labeled cells were counted followed by group comparisons (ANOVA with tukey post-hoc test).

Results: Significant reduction of a- (p<0.05) and b-wave (p=0.0001) amplitudes was noted in ERGs of all ischemic groups. The amplitudes of the bevacizumab group were comparable to the I/R group, whereas increase could be observed on amplitudes of the a- and b-wave of the ranibizumab group in comparison to I/R. Significantly fewer Brn-3a+ cells were evaluated in ischemic (p<0.001) and bevacizumab treated (p=0.019) retinas, not in ranibizumab ones compared to control. A significantly higher rate of apoptotic cells was revealed only in the I/R group (p=0.005), but not in treated groups. Ischemic and bevacizumab treated eyes displayed significantly more autophagic cells compared to control. A significantly higher rate of apoptotic cells was revealed only in the I/R group (p=0.005), but not in treated groups. Ischemic and bevacizumab treated eyes displayed significantly more autophagyotic cells (p=0.009) than the ranibizumab group. Furthermore, a significant microglial immigration and activation was detected in all ischemic groups (p<0.05) compared to control. However, a decrease of Iba1+ and ED1+ cells could be observed in ranibizumab treated retinas.

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Conclusions: Our data suggest that VEGF inhibitors have a protective effect on functionality and appearance of retinal ganglion cells after ischemic injury. In our study the efficiency of ranibizumab was greater than that of the off-label used bevacizumab. We suppose that the different effectiveness is due to the higher binding affinity and the smaller molecule size of ranibizumab which allows better retinal penetration. Thus, VEGF inhibitors represent an option to treat retinal ischemic damage.

Commercial Relationships: Marina Renner, None; Stephanie Lohmann, None; Dustin Schulte, None; Gesa Stute, None; H Burkhard Dick, None; Stephanie C. Joachim, None

Program Number: 3326 Poster Board Number: D0129
Presentation Time: 8:30 AM–10:15 AM

Clearance of Aflibercept Following Intravitreal Injection in a Rat Model

Ruti Sella1, Orly Gal-Or2, Assaf Dotan3, Mor Dachbash3, Yael Nisgav1, Dov Weinberger2, 1, Rita Ehrlich1, 2, Tami Livnat3
1Department of Ophthalmology, Rabin Medical Center, Petach-Tikva, Israel; 2Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel; 3Laboratory of Eye Research, Felsenstein Medical Research Center, Rabin Medical Center, Petach-Tikva, Israel.

Purpose: Aflibercept is known as a potent anti vascular endothelial growth factor (anti-VEGF), though little is known regarding its clearance mechanism following intravitreal injection to the eye. Our purpose was to characterize the localization and clearance of intravitreally injected Aflibercept in the eye in a rat model.

Methods: Choroidal neovascularization (CNV) was induced by diode laser photocoagulation on the right eye of 8 Brown Norway rats. 3 μL Aflibercept (25 mg/ml) was injected intravitreally on day 3 from CNV induction. Immediately after Aflibercept injection and 3, 6, 24 and 48 hours later, animals were euthanized and eyes were enucleated for immunofluorescence staining. Donkey anti-human IgG labeled with Alexa Fluor® 488 was used for Aflibercept immunoreactivity detection. Untreated eyes were used as negative control. Anti CD31 antibody was used as a marker for schlemm’s canal’s endothelial cells. Intensity of the immunofluorescence staining was analyzed qualitatively.

Results: Aflibercept immunoreactivity was detected in the cornea, iridocorneal angle, and the retina immediately after injection, and declined in a decremented manner within the following hours. Forty eight hours from the injection no Aflibercept staining was detected in the structures mentioned above.

Conclusions: Our study demonstrated the immediate accumulation of intravitreally injected Aflibercept in retina, cornea and iridocorneal angle and its presence there at least for 24 hours. Clearance of Aflibercept molecules from the eye through the iridocorneal angle and retina were shown to take place within 48 hours.

Commercial Relationships: Ruti Sella, None; Orly Gal-Or, None; Assaf Dotan, None; Mor Dachbash, None; Yael Nisgav, None; Dov Weinberger, None; Rita Ehrlich, None; Tami Livnat, None
Support: Travel Grant, ISVER (Israel Society for Vision & Eye Research)

Program Number: 3327 Poster Board Number: D0130
Presentation Time: 8:30 AM–10:15 AM

What is the biologically relevant KD for VEGF binding to ranibizumab in the eye? A comparison of in-vivo and in-vitro estimates

Norman Mazer1, Dietmar Schwab2, Laurence Hutton-Smith1, Helen M. Byrne2, Eamonn A. Gaffney3, Philip Maini4, Guido Hartmann4, Joerg Moelleken4, Christian Gassner4, Joerg T. Regula1, 4Clinical Pharmacology, Roche Innovation Center Basel, Basel, Switzerland; 2Wolfson Centre of Mathematical Biology, University of Oxford, Oxford, United Kingdom; 3Neuroscience Ophthalmology and Rare Diseases, Roche Innovation Center Basel, Basel, Switzerland; 4Large Molecule Research, Roche Innovation Center Penzberg, Penzberg, Germany.

Purpose: The high affinity binding of anti-VEGF antibodies to VEGF molecules within the eye is central to their mechanism of action in the treatment of neovascular and vascular permeability disorders of the retina. The strength of this binding is inversely related to the magnitude of the equilibrium dissociation constant, K_d, and it is presently unclear what the biologically relevant values of K_d are that characterize VEGF binding to its antibodies in ocular media. We compare our recent estimate of the in-vivo K_d value for VEGF binding to ranibizumab, a Fab fragment, with in-vitro estimates obtained using different experimental methods.

Methods: An estimate of the in-vivo K_d for VEGF binding to ranibizumab was derived from a pharmacokinetic-pharmacodynamic model of the time-course of aqueous humor levels of free VEGF following intra-vitreal injection of ranibizumab in patients with neovascular AMD (Hutton-Smith L et al., submitted to Mol Pharmacaceutics 2015). In-vitro estimates of K_d for the binding of ranibizumab to human VEGF_121 and VEGF_165 were obtained at 25 °C using the Kinetic Exclusion Assay (KinExA®) and Surface Plasmon Resonance (BIAcore®), and preliminary results with Isothermal Titration Calorimetry (ITC). In-vitro estimates of K_d at 37 °C were obtained by multiplying the 25 °C values by the ratio K_d (37 °C)/ K_d (25 °C) measured with BIAcore. The enthalpy of binding (ΔH) was estimated from this ratio using the Van’t Hoff equation.

Results: The in-vivo K_d (37 °C) K_d value (range) was estimated to be 21.3 nM (18.1 – 27.4 nM). The in-vitro K_d values at 25 °C and 37 °C are given in the Table. ΔH was estimated to be -28.9 kcal/mole.

Conclusions: There is a considerable disparity between the in-vivo estimate of K_d and the in-vitro estimates obtained by KinExA and BIAcore; whereas the preliminary in-vitro estimate obtained by ITC is comparable to the in-vivo estimate. As all methods and models are subject to assumptions and uncertainties the biologically relevant value of K_d for intravitreal VEGF binding to ranibizumab and presumably other anti-VEGF antibodies has not yet been resolved and warrants further experimental investigation. Caution should be exercised while making assessments/predictions based on in-vitro or in-vivo K_d values.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>KinExA (pM) VEGF_121</th>
<th>BIAcore (pM) VEGF_165</th>
<th>ITC (nM)/preliminary VEGF_121 and VEGF_165</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>19 (10.5 – 28.9)</td>
<td>31</td>
<td>3.2 (2 – 4.7)</td>
</tr>
<tr>
<td>37</td>
<td>126 (69 – 191)</td>
<td>205</td>
<td>21 (13 – 31)</td>
</tr>
</tbody>
</table>

In-vitro estimates (range) of KD at 25 and 37 °C for binding of ranibizumab to VEGF isoforms using KinExA, BIAcore and ITC.

Commercial Relationships: Norman Mazer, Roche; Dietmar Schwab, Roche; Laurence Hutton-Smith, None; Helen M. Byrne, None; Eamonn A. Gaffney, None.

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In the syringe and was noted to be drug-specific. Bubble formation within the syringe was proportional to the protein concentration of each anti-VEGF drug. Agents with higher protein concentration were associated with greater intra-syringe bubble volumes. The purpose of this experiment was to develop a model of bubble formation using solutions of bovine serum albumin that match the protein content of each anti-VEGF drug previously tested.

**Methods:** Nine agents were examined (DI water, ranibizumab 6 and 10 mg/mL, bevacizumab 25 mg/mL, aflibercept 40 mg/mL and BSA solutions of 6, 10, 25 and 40 mg/mL). Tuberculin syringes were loaded with 0.2ml of test solution using a filter needle. Ten trials per agent were conducted, using a new syringe for each agent. After the filter needle was replaced with a 0.5 inch 32-gauge needle, the plunger was advanced until the first fluid drop appeared. For each test solution, the volume of fluid and bubbles in the syringe was photographically measured using a microscope and digital camera (Olympus SZX16 stereo microscope, Olympus DP25 camera, CellSens software). To measure the volume of agent within each syringe, the syringe/32-gauge needle combination was weighed before and after each injection using a digital microbalance (Ohaus AV 64C). The air bubble volume was calculated by subtracting the total volume measured in the photographs from the fluid volume computed by weight for every trial.

**Results:** Bubble volumes measured within anti-VEGF drugs and BSA model solution are presented in table 1. These data are graphed with best-fit lines in figure 2. While solutions containing BSA uniformly produced slightly higher degrees of bubble formation, both anti-VEGF and BSA solutions were similarly fit to regression lines of \( R^2 = 0.98 \) and 0.97 respectively.

**Conclusions:** Protein-containing solutions have long been known to form foams. This study demonstrates that this phenomenon occurs within anti-VEGF drug solutions within the small-volume syringes we use to administer these drugs. Further, we found that air bubble formation and stability were increased with increasing protein concentration and that this phenomenon can further be studied with a low-cost protein containing solution model.

### Table 1: Air Bubble Volume measured within syringes containing anti-VEGF drugs and BSA solutions

<table>
<thead>
<tr>
<th>Protein Concentration (mg/mL)</th>
<th>Mean Air Bubble Volume (microliters)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-VEGF drugs (μg)</td>
</tr>
<tr>
<td>0 (DI water)</td>
<td>0.75±0.4</td>
</tr>
<tr>
<td>6</td>
<td>1.06±0.3</td>
</tr>
<tr>
<td>10</td>
<td>1.32±0.3</td>
</tr>
<tr>
<td>25</td>
<td>7.71±2.2</td>
</tr>
<tr>
<td>40</td>
<td>20.16±1.4</td>
</tr>
</tbody>
</table>

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Optimal Buffer for Storage of Ranibizumab at Low Concentrations

Hui Yee Chua1, Rupesh V. Agrawal5, Tina T. Wong4, Peter Preiser3, Raymond Iezzi, None

Support: Research to Prevent Blindness

Program Number: 3330 Poster Board Number: D0133
Presentation Time: 8:30 AM–10:15 AM

Optimal Buffer for Storage of Ranibizumab at Low Concentrations

Hui Yee Chua1, Rupesh V. Agrawal5, Tina T. Wong4, Peter Preiser3, Subbu Venkatraman1. 1Interdisciplinary Graduate School, Nanyang Technological University, Singapore, Singapore; 2Materials Science and Engineering, Nanyang Technological University, Singapore, Singapore; 3Biological Sciences, Nanyang Technological University, Singapore, Singapore; 4Singapore Eye Research Institute, Ocular Drug Delivery Group Singapore National Eye Centre, Singapore, Singapore; 5National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore, Singapore.

Purpose: Choroidal neovascularization is one of the contributing causes to vision loss for Age-related Macular Degeneration (AMD). Ranibizumab is an antigen-binding fragment (Fab) of a monoclonal antibody that binds to Vascular Endothelial Growth Factor (VEGF), thereby reducing neovascularization. The aim of this work is to identify the optimal storage buffer for ranibizumab at the 50% inhibition (IC50) concentrations. Ranibizumab was evaluated by quantifying the VEGF binding ability after storage in various buffers. The loss of activity due to storage in inappropriate buffers would lead to erroneous interpretation of the results.

Methods: Ranibizumab was stored for a period up to 7 days at 37°C in microtubes at concentrations between 6.25 to 50 ng/ml. The storage buffers used included: Phosphate buffer saline (PBS)-a physiologically simulating buffer; Intrinsic buffer-a cocktail containing trehalose, Tween 20 and histidine used for storing the commercial ranibizumab; Bovine Serum Albumin (BSA) buffer- BSA dissolved in PBS; Serum buffer- a cocktail reported by Genentech for diluting ranibizumab in a pharmacokinetic study consisting of BSA, Tween 20 and EDTA diluted in PBS. Ranibizumab activity in the different samples was subsequently evaluated by testing its activity to bind to VEGF using Enzyme Linked Immunosorbent Assay (ELISA) and comparing it to freshly diluted drug.

Results: Storage of ranibizumab in both PBS and BSA buffer resulted in a rapid loss of activity as measured by ELISA. Even at the highest concentration of 50ng/ml no activity could be detected in PBS (P = 0.0001) after one day of storage. In BSA buffer a similar rapid loss was observed and only 50% of activity was measurable after storage for one day. In contrast serum buffer showed no loss of activity after one day storage even at concentrations of ranibizumab as low as 6.25 ng/ml. In intrinsic buffer, no significant difference in the ranibizumab activity was detected after 7 days at concentrations as low 6.25 ng/ml.

Conclusions: In this study, ranibizumab was shown to lose its VEGF binding ability when stored at low concentrations in PBS and with BSA buffer. Both of these buffers are frequently reported to be used for ranibizumab dilution. However, VEGF binding was maintained when ranibizumab was stored in intrinsic and serum buffer. These findings will be helpful when working with ranibizumab at low nanogram concentrations during in-vitro drug release or transport.

Commercial Relationships: Hui Yee Chua, None; Rupesh V. Agrawal, None; Tina T. Wong, None; Peter Preiser, None; Subbu Venkatraman, None

Support: NHG Thematic Grant/13008

Program Number: 3331 Poster Board Number: D0134
Presentation Time: 8:30 AM–10:15 AM

No excuses. Bevacizumab should be first choice in AMD

Freekje Van Asten1, Charlotte Michels2, Carel C. Huyng1, Gert Jan van der Wilt2, B. Jeroen Klevering1, Marooska M. Rovers1, Janneke P. Grutters1. 1Ophthalmology, Radboud umc, Nijmegen, Netherlands; 2Health Evidence, Radboud umc, Nijmegen, Netherlands.

Purpose: Bevacizumab is an effective, safe and cheap treatment option for neovascular age-related macular degeneration (AMD). However, bevacizumab is not registered for AMD. Therefore, in some countries ophthalmologists either voluntarily choose or are forced to use the equally effective but expensive drugs ranibizumab and aflibercept. Here we describe the economic consequences of this dilemma surrounding AMD treatment.

Methods: We modelled cost-effectiveness of treatment with ranibizumab (as-needed), aflibercept (bimonthly) and bevacizumab (as-needed). The drug with the most favourable cost-effectiveness profile compared to bevacizumab was used for threshold analyses. First, we determined how much we overpay per injection. Second, we calculated the required effectiveness to justify the current price and what a reasonable price is for a drug that leads to optimal vision. Finally, we estimated how much we overspend on health care when bevacizumab is not first choice.

Results: Bevacizumab treatment costs €27,087 ($28,799) per year, approximately €4,000 ($4,250) cheaper than aflibercept and €6,400 ($6,600) cheaper than ranibizumab. With similar effectiveness for all drugs, bevacizumab was clearly the most cost-effective. Aflibercept was chosen for threshold analyses. Aflibercept costs €943 ($1,003) per injection, but we determined that the acceptable price is actually €533 ($567). Alternatively, at its current price, aflibercept should yield about twice the visual gain. Even when optimal vision can be achieved, the maximum price for any treatment is €37,453 ($39,820) per year. Most importantly, Europe wastes €820 million and the US wastes $570 million on AMD treatment when choosing aflibercept over bevacizumab.

Conclusions: Bevacizumab is undoubtedly the most cost-effective treatment for AMD, yet it is not the standard of care across Europe and the US. The registered drugs ranibizumab and aflibercept cause huge overspending without additional health benefits. Health
Commercial Relationships: Freekje Van Asten, None; Charlotte Michels; Carel C. Hoyn, None; Gert Jan van der Wilt, None; B. Jeroen Klevering, None; Maroeska M. Rovers, None; Janneke P. Grutters, None

Program Number: 3332 Poster Board Number: D0135
Presentation Time: 8:30 AM–10:15 AM
Factors associated with retreatment after photodynamic therapy combined with intravitreal ranibizumab for polypoidal choroidal vasculopathy

Purpose: To investigate the retreatment incidence and its risk factors within 60 months after photodynamic therapy (PDT) combined with intravitreal ranibizumab (IVR) for treatment-naïve polypoidal choroidal vasculopathy (PCV).

Methods: We retrospectively reviewed the medical records of 61 eyes from 60 patients with PCV, who were followed-up for at least 12 months after the combination therapy. Retreatment including IVR or the combination therapy was conducted if residual or recurrence exudative changes were present. We investigated whether baseline clinical and genetic factors including ARMS2 A69S and CFH I62V, were associated with retreatment after the initial treatment.

Results: During follow-up period (mean: 44±13 months, median 48 months), 46 eyes (75.4%) received the retreatment. Survival analysis revealed that survival proportion was 59%, 41%, 31%, 24%, and 20% at 12-, 24-, 36-, 48- and 60-month visit, respectively. Median and mean retreatment free period was 15.0(95% confidence interval (CI): 7.4-22.7) and 24.9(95% CI: 19.3-30.6) months, respectively. Mean best-corrected visual acuity (BCVA) significantly improved throughout follow-up periods except at 48-month visit. Cox regression analysis revealed that older age (P=0.011, hazard ratio 1.05 confidence interval 1.01-1.10) and male (P=0.018, hazard ratio 2.47 confidence interval 1.05-5.61) was associated with retreatment.

Conclusions: Visual outcomes 5 years after PDT combined with IVR were relatively favorable. Retreatment was required for about 80% eyes within 60 months after the combined therapy for PCV. Retreatment was associated with older age and male.

Commercial Relationships: Wataru Kikushima, None; Yoichi Sakurada, None; Atsushi Sugiyama, None; Naohiko Tanabe, None; Seigo Yoneyama, None; Hiroyuki Iijima, None

Program Number: 3333 Poster Board Number: D0136
Presentation Time: 8:30 AM–10:15 AM
REAL LIFE SETTING TREATMENT BY ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR FOR WET AGE-RELATED MACULAR DEGENERATION: INACTIVATION OF LESION AND LONG TERM OUTCOMES
Mohamed Maher Haouas1, 2, Gilles Thuret3, 4, Philippe GAIN5, Michel Paques5, Jose Sahel7, Jean-Francois GIRMENS8, NOVARTIS (C), BAYER (C)

Purpose: To report the percentage of treatment discontinuation because of inactivation of lesion and the long-term visual outcomes for patients receiving a real life setting treatment by anti-vascular endothelial growth factor (VEGF) for neovascular age-related macular degeneration (AMD).

Commercial Relationships: Mohamed Maher Haouas, None; Gilles Thuret, None; Philippe GAIN, None; Michel Paques; Jose Sahel, None; Jean-Francois GIRMENS, NOVARTIS (C), BAYER (C)
Real-world outcomes of switching AntiVEGF treatment from ranibizumab to aflibercept for neovascular age-related macular degeneration (nAMD): UK multicentre study

**Purpose:** AntiVEGF injections have improved clinical outcomes in treatment naïve nAMD patients. There is a paucity of information on large cohorts of patients switched from one antiVEGF agent to another. This study set out to evaluate outcomes from large numbers of patients from multiple centres to evaluate the clinical benefit in terms of visual stabilisation or improvement over time.

**Methods:** All patients with nAMD whose treatment was switched from ranibizumab to aflibercept were included in the study. Prospectively entered visual acuity data were collected and extracted from Medisoft, an electronic patient record used at 16 centres in the UK. Data collection is ongoing, the data cut presented is until the end of October 2015, providing 2-year follow up.

**Results:** The mean visual acuity at the point of switch in 3770 eyes was 57.6 ETDRS letters, 58.6 at 6 months (1933 eyes), 57.7 at 12 months (1322 eyes), 57.8 at 18 months (1114) and 57.6 letters at 24 months. The mean visual acuity had been 61.1 letters 24 months prior to switch in 1122 eyes and 60.2 at 12 months prior to switch (1830 eyes). There was a mean decline of 3.5 letters over 24 months prior to switch. There was no change in mean visual acuity at 24 months after switch to aflibercept.

**Conclusions:** The visual acuity of patients switched to aflibercept from ranibizumab remained stable over 24 months post switch. Aflibercept appears to be effective in stabilising visual acuity as a sequential treatment in patients where visual acuity had worsened on ranibizumab treatment.

**Commercial Relationships:** Faruque D. Ghanchi, Novartis (R), Bayer (R); Nishal Patel, James S. Talks, Novartis (R), Bayer (R); Andrew J. Lotery, Novartis (R), Bayer (R); Sobha Sivaprasad, Novartis (C), Bayer (C), Novartis (R), Novartis (F), Bayer (F); Clare Bailey, Novartis (R), Bayer (R); Rob Johnston, Novartis (R), Bayer (R), Medisoft ltd (I); Martin McKibbin, Novartis (R), Bayer (R)

Program Number: 3335 Poster Board Number: D0138
Presentation Time: 8:30 AM–10:15 AM
Real-world treatment patterns in injection cost and frequency for ranibizumab versus aflibercept in patients with wet age-related macular degeneration: A 2-year US claims analysis

**Purpose:** To compare the real-world treatment patterns, specifically, frequency and cost of intravitreal injections of two anti-vascular endothelial growth factor (anti-VEGF) agents, ranibizumab (RBZ) and aflibercept (AFL), for treatment of wet age-related macular degeneration (AMD) in treatment-naïve (TN) and previously-treated (PT) patients over 2 years.

**Methods:** This retrospective US claims study included TN or PT patients who initiated RBZ or AFL treatment (index date [ID]) for AMD between 11-18-2011 and 7-31-2015. Patients were aged ≥18 years on the ID and were required to have continuous eligibility for 12 months (12M) prior to ID and for 12-24 months (24M) following ID without switching to another anti-VEGF agent. Injection frequency and cost for RBZ vs. AFL were compared at 12M and 24M using multivariable Poisson quasi-likelihood regressions (treating RBZ as reference) and multivariable generalized linear models with a log link and gamma distribution, respectively. All models were adjusted for patient demographics and clinical characteristics.

**Results:** Over 12M, TN AMD patients receiving RBZ (N=2260) and AFL (N=1256) had a comparable unadjusted mean number of injections (5.4 vs. 5.4, adjusted incidence rate ratio [IRR] = 0.99, 95% confidence interval [CI] = 0.95 to 1.03, P = 0.558) and marginally lower injection costs with AFL vs. RBZ ($10,417 vs. $11,032, adjusted cost ratio [CR] = 0.93, 95% CI = 0.89 to 0.98, P = 0.008). At 24M, injection frequency and cost were comparable between RBZ (N=1018) and AFL (N=482) in TN patients (7.6 vs. 8.1, IRR = 1.06, 95% CI = 0.98 to 1.14, P = 0.168; $15,393 vs. $15,410, CR = 0.99, 95% CI = 0.89 to 1.09, P = 0.832). Over 24M, PT AMD patients receiving RBZ (12M N=873; 24M N=344) or AFL (12M N=1990; 24M N=847) had comparable injection frequency (12M 5.7 vs. 5.8, IRR = 0.99, 95% CI = 0.96 to 1.04, P = 0.984; 24M 9.3 vs. 9.6, IRR = 1.00, 95% CI = 0.92 to 1.08, P = 0.926) and costs (12M $11,589 vs. $11,521, CR = 0.97, 95% CI = 0.92 to 1.03, P = 0.393; 24M $18,548 vs. $19,202, CR = 1.03, 95% CI = 0.92 to 1.14, P = 0.629).

**Conclusions:** This 2-year claims-based analysis shows that the real world treatment patterns for treatment-naïve and previously-treated patients, given RBZ or AFL for AMD, are comparable in costs and injection frequency.

**Commercial Relationships:** Szilard Kiss, Avalanche (C), Alimera (C), B&K (C), Regeneron (C), Genentech-Roche (C), Allergan (C), Alcon (C); Yamina Rajput, Genentech; Carlos Quezada Ruiz, Genentech; Kathleen Wilson, Genentech (C); Alice Huang, Genentech (C); David M. Smith, Genentech (C); Helen Varker, Genentech (C); Stephen S. Johnston, Genentech (C)

Support: Genentech, Inc., South San Francisco, CA, provided support for the study and participated in the study design; conducting the study; and data collection, management, and interpretation.

Program Number: 3336 Poster Board Number: D0139
Presentation Time: 8:30 AM–10:15 AM
Factors associated with poor response to aflibercept after switching from ranibizumab or bevacizumab in neovascular age-related macular degeneration (AMD)

**Purpose:** With the introduction of aflibercept as a treatment for neovascular AMD, physicians have switched patients on ranibizumab or bevacizumab who failed to improve visual acuity with the goal of a better response. While some patients improved on aflibercept, others developed worse vision. The purpose of this study was to determine factors associated with worse visual outcomes after switching.

**Methods:** A retrospective review was performed of 248 patients treated with aflibercept from November 2011 to August 2014. Visual acuity was examined at the time of the switch, one month, three months, and 12 months after. Patients who improved visual

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Acuity after switching to aflibercept were compared to patients who lost vision. Spectral domain optical coherence tomography (SD-OCT) imaging was performed at the time of the switch. SD-OCT parameters such as vitreomacular adhesions, epiretinal membrane, sub-retinal fluid, intra-retinal fluid, pigment epithelial detachment, integrity of the ellipsoid zone, subretinal CNV or scar, geographic atrophy, and central cube thickness as well as central subfield thickness were used as predictors of worsening—in addition to age, gender, race, BMI, obesity (BMI >30), smoking, co-morbid conditions (hypertension, diabetes, malignancies), use of anti-inflammatory medication (bromfenac, trimacinolone acetoniode), number of previous injections of ranibizumab and bevacizumab, and use of Age-Related Eye Disease Study supplements—for the analysis. Demographic and SD-OCT imaging findings were compared between responders and non-responders, using univariate (X2, Wilcoxon Rank Sum, T-Test) and multivariate (nominal logistic) analysis. Statistical significance was taken for p < 0.05 and trending significance were taken for 0.05 < p < 0.10.

**Results:** Twenty-five patients (29 eyes) improved visual acuity after switching, and 21 patients (23 eyes) lost vision after the switch. Patients who lost vision had significantly higher body mass index (BMI) (p = 0.013 and rate of obesity (p=0.0014). Geographic atrophy at the switch was also identified as a significant predictor (p = 0.038).

**Conclusions:** Higher BMI and preexisting geographic atrophy may be potential indicators for poor response to aflibercept after switching from ranibizumab or bevacizumab.

**Commercial Relationships:** Sarah Cheng, None; Theodore Leng

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**Program Number:** 3337 **Poster Board Number:** D0140 **Presentation Time:** 8:30 AM–10:15 AM

**Safety and complications of Intravitreal injections performed over 8 years at a tertiary eye centre in Singapore**

**Yanping Xu, Colin S. Tan. Ophthalmology, National Healthcare Group Eye Institute, Singapore, Singapore.**

**Purpose:** There has been a rapid rise in the use of intravitreal injections such as anti-vascular endothelial growth factors (anti-VEGF), performed over the past few years for the treatment of ocular neovascular diseases. This study aims to review the systemic and ocular adverse events amongst patients treated at a tertiary eye centre over a period of 8 years and compare the rates to major randomized control trials.

**Methods:** A retrospective review of all intravitreal injections of anti-VEGF performed over an 8-year period at a tertiary eye care centre in Singapore was done. We report the frequency of systemic and ocular adverse events and compared it amongst the various anti-VEGF agents.

**Results:** A total of 14,001 intravitreal injections were performed on 2225 patients from January 1, 2007 to December 31, 2014, and this included 9992 bevacizumab (71.4%), 3306 ranibizumab (23.6%) and 703 aflibercept (5.0%) injections. The mean age of the patients in the study was 68.5 ± 11.8 years (median 68.0 years, range: 21 to 102 years). There were 1266 male and 959 female patients in this study. The majority of the patients in our study were of Asian descent, with 1715 (77.0%) Chinese, 182 (8.2%) Malay, 182 (8.2%) Indian and 146 (6.6%) of other races. Systemic complications related to treatment were: 26 (1.17%) deaths (from any cause), of which 11 (0.49%) were from fatal thromboembolic events, 7 (0.31%) non-fatal thromboembolic events and 2 (0.09%) serious nonocular hemorrhage. Ocular complications included 1 (0.007%) endophthalmitis, 3 (0.021%) traumatic cataracts and 1 (0.007%) retinal detachment.

Overall, there was no statistical significance between rates of thromboembolic events and death between Ranibizumab (Lucentis), Bevacizumab (Avastin) and Aflibercept (Eylea).

**Conclusions:** The systemic and ocular complications associated with intravitreal injections among Asian patients at a tertiary eye centre are relatively low, and reflect the safety of the treatments. There is no significant difference between the rates of adverse events between different anti-VEGFs.

**Commercial Relationships:** Yanping Xu, None; Colin S. Tan, None

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Program Number: 3339  Poster Board Number: D0142
Presentation Time: 8:30 AM–10:15 AM
Evaluating of cytotoxicity of Pazopanib on proliferation of vascular endothelial growth factor enriched choroidal vascular endothelial cells
Purpose: Ranibizumab, Bevacizumab and Afilbercept are currently approved anti vascular endothelial growth factor (VEGF) agents for the management of exudative age related macular degeneration (AMD). However they are expensive and need repeated intravitreal injections due to limited duration of action. Pazopanib (FDA approved), a tyrosine kinase inhibitor that blocks the receptors of VEGF is effective in management of renal cell carcinoma. through inhibition of VEGF. In this study we evaluated the cytotoxicity of varying doses of Pazopanib on VEGF enriched choroidal vascular endothelial cells (CVECs)
Methods: Proliferating CVECs (enriched with VEGF 50 ng/ml) were treated with escalating doses of pazopanib (10, 50, 100, 250 µM). Cell proliferation changes were analyzed with water soluble tetrazolium salts (WST-1) assay. Cytotoxicity in response to pazopanib was evaluated with trypan blue exclusion assay at 48h, 72h, 1 week. Simultaneously reactive oxygen species levels were measured using dihydorhodamine 123 at similar intervals. Human retinal pigment epithelial cells (HRPEs) served as controls.
Results: Pazopanib inhibited the proliferation of VEGF enriched CVECs treated with varying doses of pazopanib (10, 50, 100, 250 µM) in a dose and time dependent manner. CVECs showed a significant decrease in the cell proliferation after one week treatment with pazopanib compared to controls. The CVECs showed a decrease in cell proliferation by 12.2% (p<0.0001), 57% (p<0.0001), 61.9% (p<0.00001), 90.7% (p<0.0001) in comparison to control cells respectively with WST-1 assay. Trypan blue exclusion assay also revealed similar decrease in CVECs proliferation 18.2% (p=0.24), 19% (p=0.21), 46.6% (p=0.0014), 91.3% (p=0.0001) compared to control cells. Reactive oxygen species levels increased significantly in CVECs in a dose dependent manner i.e 138.6% (p=0.02), 148.9% (p=0.003), 153.9% (p=0.001), and 169.9% (p<0.0001) respectively compared to control cells.
Conclusions: Pazopanib inhibited cell proliferation of VEGF enriched CVECs significantly compared to controls in a dose and time dependent fashion and can be potentially effective in controlling subretinal choroidal neovascular membrane associated with AMD.
Commercial Relationships: K. V. Chalam, None; Bharani Krishna Mynampati Arundithya, None; Kumar Sambhav, None

Program Number: 3340  Poster Board Number: D0143
Presentation Time: 8:30 AM–10:15 AM
A real-world evaluation of frequency of ranibizumab and aflibercept deliveries for treatment-naïve patients with neovascular age-related macular degeneration: 12-month results from the French LYVE study survey
Oudy Semoun1, Rocio Blanco-Garavito1, Salomon Y. Cohen1, Laetitia Finzi1, Camille Maurin1, Eric H. Soutiel1. Ophthalmology, Centre Hospitalier Intercommunal de Créteil, Créteil, France; Centre Imagerie et Laser, Paris, France; 1Retine, Novartis Pharma SAS, Rueil-Malmaison, France.
Purpose: The LYVE survey employed a unique design that used two databases in France to evaluate the frequency of ranibizumab (RBZ) and aflibercept (AFL) deliveries over the 12-month follow-up period for treatment-naïve patients with neovascular age-related macular degeneration (nAMD) in routine medical practice.
Methods: LYVE was an observational, prospective, longitudinal survey analyzing 12-month data from two databases that recorded delivered products and patients’ information: a nationally representative pharmacy records database and a pharmacy-based questionnaire system. Treatment-naïve patients with nAMD who received their first RBZ/AFL prescription between October 2013 and July 2014 were enrolled (Figure 1). The primary objective was to evaluate the overall frequency of RBZ and AFL deliveries in a real-life setting in treatment-naïve patients with nAMD. Key secondary objectives were to evaluate the proportion of patients with a treatment switch (changed to a new treatment and maintained the same) or switch-back (changed from new treatment to the original treatment).
Results: Of the 2023 screened patients, 466 treatment-naïve patients (RBZ, n=314; AFL, n=152) were enrolled. Of the 400 patients with unilateral nAMD (RBZ, n=273; AFL, n=127), 220 treatment-naïve patients (RBZ, n=145; AFL, n=75) were analyzed during the 12-month follow-up. The baseline patient characteristics (age, gender) were well-balanced in both RBZ and AFL groups. The mean number of deliveries was 4.7, with no significant differences observed between the treatment groups (P=0.321; Figure 2). The mean time between RBZ and AFL deliveries was non-statistically different during the 12-month follow-up (P=0.357). No significant differences were observed between the two groups in terms of the proportion of patients who had a treatment switch (RBZ, n=31; AFL, n=8) or switch-back (RBZ, n=7; AFL, n=1).
Conclusions: LYVE represents a unique national sample of real-life data of nAMD treatment patterns in France. No statistically significant differences were observed between the treatment-naïve patients in terms of the frequency of RBZ and AFL deliveries over the 12-month follow-up period.

Data collection methodology—Constitution of a unique national sample

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Time between ranibizumab and aflibercept deliveries

**Commercial Relationships:** Oudy Semoun, Novartis (C), Bayer (C); Rocío Blanco-Garavito, Novartis (C); Salomon Y. Cohen, Thea (C), Novartis (C), Bayer (C), Allergan (C), Alcon (C); Laetitia Finzi, Novartis Pharma SAS; Camille Maurin, Novartis Pharma SAS; Eric H. Souied, Thea (C), Novartis (C), Bayer (C), Allergan (C)

**Support:** Novartis Pharma SAS

**Program Number:** 3341

**Poster Board Number:** D0144

**Presentation Time:** 8:30 AM–10:15 AM

Angiogenesis Agents Levels After Bevacizumab Intravitreal Injection in Patients with Neovascular Age-related Macular Degeneration

**Thiago Cabral1, 2, Luiz H. Lima1, Julia Polido1, Everton P. Correia3, Pedro D. Serracarabassa4, Caio V. Regatieri5, Belfort Rubens6**

1 Ophthalmology, UNIFESP, Vitoria/ES, Brazil; 2 Ophthalmology, UFES, Vitória, Brazil; 3 Ophthalmology, HSPE/IAMSPE, Sao Paulo, Brazil.

**Purpose:** To evaluate the concentration of nineteen angiogenic biomarkers in the aqueous humor before and after intravitreal injection of bevacizumab in treated eyes with neovascular age-related macular degeneration (AMD).

**Methods:** In this prospective study, 23 eyes of 23 patients with choroidal neovascularization secondary to neovascular AMD were treated with three initial intravitreal injections of bevacizumab, according to PrONTON dosing regimen. Aqueous humor samples were obtained by anterior chamber paracentesis before each intravitreal injection (IVB). Nineteen vasogenic biomarkers [angiopoietin-2, bone morphogenetic protein-9 (BMP-9), epidermal growth factor (EGF), endoglin, endothelin-1, fibroblast growth factor (FGF-1 and FGF-2), follistatin, granulocyte-colony stimulating factor (G-CSF), heparin-binding EGF-like growth factor (HB-EGF), hepatocyte growth factor (HGF), interleukin-8 (IL-8), leptin, placental growth factor (PLGF), vascular endothelial growth factor (VEGF-A, VEGF-C, VEGF-D) and tissue inhibitor of metalloproteinase (TIMP-1 and TIMP-2)] concentration in the aqueous humor were measured using an ELISA assay.

**Results:** VEGF-A level was elevated in all patients at baseline before the initiation of IVB injection, and a significant decrease in its level was observed at 1 and 2 months follow-up periods immediately before IVB injections. The mean ± SD aqueous concentration of VEGF-A was 79.91 ± 48.17 pg/mL at baseline, 7.660 ± 3.523 pg/mL at 1 month and 7.622 ± 3.423 pg/mL at 2 months follow-up periods (P < 0.0001). Seven study vasogenic biomarkers (VEGF-A, angiopoietin-2, endostatin-1, follistatin, HB-EGF, HGF, IL-8) had statistically significant increase in their levels after intravitreal injection of bevacizumab. The other eleven study biomarkers levels (VEGF-D, BMP-9, EGF, endoglin, FGF-1, FGF-2, G-CSF, leptin, PLGF, TIMP-1 and TIMP-2) did not show statistically significant difference.

**Conclusions:** Our investigation suggests a correlative relationship between VEGF-A and seven other study biomarkers in the eye with regard to expression that may have therapeutic significance. Aqueous levels of VEGF-C, angiopoietin-2, endostatin-1, follistatin, HB-EGF, HGF, IL-8 significantly increased with the decrease of VEGF-A, suggesting new pathways for the neovascularization. SUCH UPREGULATED ANGIOGENIC BIOMARKERS MAY BE POTENTIAL NEW TREATMENT TARGETS FOR CNV DUE TO AMD.

**Commercial Relationships:** Thiago Cabral, None; Luiz H. Lima, None; Julia Polido, None; Everton P. Correia, None; Pedro D. Serracarabassa, None; Caio V. Regatieri, None; Belfort Rubens, None

**Program Number:** 3342

**Poster Board Number:** D0145

**Presentation Time:** 8:30 AM–10:15 AM

Real-world one year outcomes of a switch to aflibercept from ranibizumab in neovascular age related macular degeneration


NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, United Kingdom.

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Methods: A retrospective study on consecutive patients who switched from ranibizumab to aflibercept from October 2013 till November 2013. A minimum of 12 ± 1 month of follow-up was required. Visual acuity (VA) was collected at baseline and at the end of the follow-up. Optical Coherence Tomography (OCT) images, acquired with a single device (Topcon 3D-2000, Topcon) were analysed by a single grader. Central subfield thickness (CST), presence of intra retinal fluid (IRF), sub retinal fluid (SRF) and pigment epithelium detachment (PED) were collected.

Results: 110 patients were included in the study. The mean age was 78.5±7.0 with 59.1% of them females. The mean number of previous ranibizumab injections was 8.00 (95% CI 7.58-8.42). The mean number of aflibercept injections was 6.44 (95% CI 6.15-6.72). At baseline, the mean VA was 64.01 letters (95% CI 61.21-68.80) and CST was 271.79μm (95% CI 258.63-284.95). At 12 months post-switch, mean VA was 63.05 letters (95% CI 59.80-66.31) and CST was 246.33μm (95% CI 235.03-257.62). The difference in CST from baseline was statistically significant (p<0.001) but not for VA (p=0.3249). The difference in VA after 12 months was not significantly associated with presence of IRF (p=0.2983), SRF (p=0.7383) and PED (0.9171) at baseline. The presence of IRF was associated with worse VA at baseline (p<0.001) and at 12 months (p<0.001).

Conclusions: The switch from ranibizumab to aflibercept is a viable option in nAMD due to cost-effectiveness maintained the VA and achieved a significant reduction in CST at 12 months of treatment in our cohort of patients.

Commercial Relationships: Maria C. Citu, None; Roxanne R. Crosby-Nwaoib, None; Maria Eleftheriadou, None; Clara Vazquez-Alfageme, Luke Nicholson, None; Sobha Sivaprasad, Novartis (C), Bayer (C), Roche (F), Novartis (F), Allergan (C), Allergan (F), Bayer (F); Philip Hykin, Novartis (C), Bayer (C), Novartis (F), Allergan (C), Allergan (F), Bayer (F); Robin D. Hamilton, Novartis (C), Ellex (R), Novartis (R), Bayer (C), Bayer (R), Novartis (F), Ellex (C), Allergan (R), Bayer (F), Allergan (C)

Program Number: 3343 Poster Board Number: D0146 Presentation Time: 8:30 AM–10:15 AM
Real World U.S. Outcomes of Anti-Vascular Endothelial Growth Factor (VEGF)Therapy in Neovascular AMD (NAMD): Risk of Vision Loss is Greatest in Patients with Better Baseline Visual Acuity

Forbes Huang1, Keith Westby1, David F. Williams2, Thomas A. Ciulla1, Sandi Zaveri1, Samir Patel1. 1Ophthotech, Princeton, NJ; 2Vestrum Health, Naperville, IL.

Purpose: European studies of anti-VEGF therapy for neovascular AMD (NAMD) have shown that visual outcomes in the “real world” do not achieve those shown in randomized clinical trials (RCT). While the cause of this discrepancy is unknown, patient characteristics and under treatment associated with discontinuous treatment regimens are implicated. We explored this issue by analyzing a large database composed of aggregated, longitudinal electronic medical records (EMR) from a demographically diverse sample of US retina specialists.

Methods: The HIPAA-compliant Vestrum Health Retina Database was utilized. Inclusion required at least 3 monthly anti-VEGF injections for naive NAMD patients in the first 4 months between January 2011 and July 2013 with availability of 6 to 24 months of follow-up data, ending July 2015 (n=2,213). The eyes were divided into 3 cohorts: those with records including visual acuity (VA) measurements up to and including 6-months but not beyond (“6-month cohort”, n=97), up to 12-months but not beyond (“12-month cohort”, n=195), and those up to and including 24 months (“24-month cohort”, n=1,921), with each cohort being mutually exclusive of one another. VA outcomes were assessed on each cohort as a whole, and also stratified by baseline VA.

Results: Best VA outcomes were evident in the 24-month cohort, followed by the 12-month and finally the 6-month cohorts. When stratified by baseline VA of 20/200 or worse, 20/70-20/200, 20/40-20/70, and 20/40 or better, the final mean change in number of letters gained or lost in the 24-month cohort was +19.9, +2.6, +1.2, and -5.2 letters respectively, in the 12-month cohort +8.9, -1.3, -5.6, and -4.5 letters respectively, and in the 6-month cohort +8.8, -4.6, -1.9, and -5.2 letters respectively.

Conclusions: This analysis corroborates prior observations that visual outcomes following anti-VEGF therapy for NAMD in the “real world” do not achieve those seen in RCT. Eyes with better baseline VA are disproportionately affected, with loss of vision observed in eyes with baseline VA of 20/70 or better. Duration of treatment and/or follow-up appear to correlate with best visual outcome. This observation highlights the need for more intensive therapy and treatment compliance in NAMD, especially those patients with better baseline VA.

Commercial Relationships: Forbes Huang, Ophthotech (I), Ophthotech; Keith Westby, Ophthotech (I), Ophthotech; David F. Williams, Vestrum Health (I), Vestrum Health; Thomas A. Ciulla, Ophthotech (I), Ophthotech; Sandi Zaveri, Ophthotech (I), Ophthotech; Samir Patel, Ophthotech (I), Ophthotech

Program Number: 3344 Poster Board Number: D0147 Presentation Time: 8:30 AM–10:15 AM
Variation in Ophthalmologist Use of Anti-VEGF Therapy Among Medicare Beneficiaries

Rachel Thakore1, Paul B. Greenberg2, Dustin French3, Jess J. Behrens3. 1Warren Alpert Medical School of Brown University, Providence, RI; 2Department of Ophthalmology and the Center for Healthcare Studies, Feinberg School of Medicine, Northwestern University, Chicago, IL; 3Veterans Affairs Health Services Research and Development Service, Chicago, IL;

Purpose: The type of anti-vascular endothelial growth factor (anti-VEGF) therapies used by ophthalmologists can vary considerably, impacting the costs of care. Using the recently released Medicare physician utilization data, we analyzed geographic trends in the use of anti-VEGF therapy amongst ophthalmologists across a two-year period (2012-2013).

Methods: Using Healthcare Common Procedure Coding System codes, we identified ophthalmologists who billed for ranibizumab (J2778), bevacizumab (J9035), and aflibercept (J0178/Q2046) in the 2012 and 2013 Medicare Provider Utilization and Payment Data: Physician and Other Supplier Public Use Files. We classified ophthalmologists to hospital referral regions (HRRs), urban/ rural status, and Census regions using zip codes. We used ArcGIS (Redlands, CA, USA) to map the percentage of physicians in each

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HRR that used each anti-VEGF drug. We conducted chi-squared tests to determine 1) variation based on year, Census region, urban/rural status, and 2) geographic changes between 2012 and 2013.

**Results:** The Figure shows geographic variation based on HRRs. Aflibercept was used by the least number of physicians in 2012 (57.0%; n=1359) but was the most widely used medication in 2013 (69.6%; n=1835). In the west, bevacizumab was used by more ophthalmologists (91.5%; n=606) than aflibercept (57.3%; n=379) and ranibizumab (52.4%; n=347). In the Midwest, more ophthalmologists used aflibercept (81.2%; n=423) and ranibizumab (77.0%; n=401) than bevacizumab (19.4%; n=101). There was significant variation in anti-VEGF drug use based on the year (p<0.001), Census region (p<0.0001), and urban/rural status of the ophthalmologist (p=0.0001) [Table]. From 2012 to 2013, the number of ophthalmologists using bevacizumab increased from 9.9% (43/434) to 19.0% (95/500) in the Midwest and 84.3% (493/585) to 90.2% (573/635) in the west (p<0.001).

**Conclusions:** From 2012 to 2013, there was significant geographic variation in anti-VEGF drug use among ophthalmologists as well as significant changes in prescribing patterns. Further research is needed to identify the major determinants of this geographic variation and how these trends may impact future Medicare costs.

**Anti-Vascular Endothelial Growth Factor Drug(s) Used by the Greatest Percentage of Ophthalmologists per Hospital Referral Regions, 2012/2013.**

**Variation in Anti-VEGF drugs by year, urban/rural status, and Census region**

**Commercial Relationships:** Rachel Thakore; Paul B. Greenberg, None; Dustin French, None; Jess J. Behrens, None

**Program Number:** 3345 **Poster Board Number:** D0148 **Presentation Time:** 8:30 AM–10:15 AM

**Patient satisfaction with nurse delivered intravitreal injections**

Adam Mapani, Yasir Khan. Medical Retina Service, Moorfields Eye Hospital, London, United Kingdom.

**Purpose:** Controversy exists whether nurse practitioners are substituting ophthalmologists in the delivery of intravitreal injections in an ever evolving retina care landscape. We performed a patient satisfaction survey and semi structured interviews to study patient satisfaction with nurse led intravitreal injection service.

**Methods:** Both qualitative and quantitative was applied. At least 500 new (first time) and follow up patients with various spectrum of conditions diabetic macular oedema, retina vein occlusion and age related macular degeneration attending the injection service were recruited to complete a structured, self-administered questionnaire. The survey examined patient satisfaction and experience of nurse practitioners, competence and knowledge, service efficiency, comparison of doctor/nurse injection delivery, practitioner attitude and explanation and demographic distribution. Semi structured
interviews were contacted with a minimum of 40 patients who did not participate in the cross sectional survey study. Semi Structured interviews explored patient perception, experience and understanding of nurse delivered injections how best this is delivered in the injection service. All interviews were audio-taped, transcribed verbatim and analysed with the inductive thematic approach.

**Results:** Mean patient satisfaction score (n =500)

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<thead>
<tr>
<th>Scale</th>
<th>Mean score</th>
<th>Maximum</th>
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<tr>
<td>General Patient satisfaction with nurse injections</td>
<td>4.5</td>
<td>5</td>
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<tr>
<td>Practitioner Explanation to the patient injection process</td>
<td>4.8</td>
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<tr>
<td>Quality of time spent with the Nurse practitioner during procedure</td>
<td>4.65</td>
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<td>Nurse Practitioner Competence</td>
<td>4.8</td>
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<td>Technical Quality</td>
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<td>Provision of information and communication</td>
<td>4.8</td>
<td></td>
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<tr>
<td>Interpersonal manner by the Practitioner</td>
<td>4.8</td>
<td></td>
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<tr>
<td>Nurse practitioner /Doctor preference</td>
<td>4.4</td>
<td></td>
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</tbody>
</table>

**Conclusions:**

In the United Kingdom, nurse practitioners play a significantly increasing role in the management of retina care and delivery of intravitreal injections. Patients reported positive experience with nurse practitioner delivered injections. This survey aimed to assess patient satisfaction with nurse practitioners and confirmed; quality of time they spent with practitioners, rapport building with the same practitioner every visit, competence and technical skills of the injections were highly rated with participants. Trained nurse practitioners can contribute towards patient holistic care, better clinical outcomes, and potential quality improvement service.

**Commercial Relationships:** adam mapani, Yasir Khan, None

**Program Number:** 3346 **Poster Board Number:** D0149
**Presentation Time:** 8:30 AM–10:15 AM

**Outcomes of an intravitreal injection clinic**

Elizabeth Atchison¹, Sophie J. Bakri¹, Ahmed F. Omar²

¹Ophthalmology, Mayo Clinic, Rochester, MN; ²Ophthalmology, UT Southwestern Medical Center, Dallas, TX.

**Purpose:** To examine the safety outcomes of an intravitreal injection only clinic where patients needing chronic anti-VEGF therapy are treated with injections at a predetermined interval for a set number of injections without an accompanying clinic visit.

**Methods:** A retrospective chart review of all patients with exudative macular degeneration treated in an intravitreal injection clinic over a 6 year period. Data on the date, injected drug, laterality, whether it was part of a pre-assigned cycle and whether it was an injection-only visit or in conjunction with a clinic visit was recorded for each injection. For every patient with an interruption of an injection cycle the reason the cycle was discontinued was gathered from the chart. For each patient requiring an urgent (non-routinely scheduled) clinic visit, diagnoses made at such visits was recorded. All patients who changed laterality of treatment or who went from treating one eye to both eyes had their charts reviewed for new diagnosis of exudative AMD in the fellow eye.

**Results:** 556 patients received 4386 injections in the injection only clinic in a total of 1524 injection cycles. 106 cycles (74) were interrupted. The most common causes for interruption were: 32 for decreased vision in the injected eye, 23 for decreased vision in the fellow eye, 6 for flashing, 5 for pain, and 2 for irritation in the non-injected eye. Of patients who had an interruption of the cycle, 32 had a new diagnosis (most common: 6 abrasions, 6 exudative AMD in fellow eye). Of those with a diagnosis of exudative AMD in the fellow eye on an urgent visit, 3 had a sudden vision change within one week of being seen, 1 had 10 days of symptoms, 1 had 3 weeks of symptoms and one did not have a date of sudden change recorded. Four patients had been seen with a full clinic and OCT visit less than 1 month before. There were 6 instances of conversion to exudative AMD found in the other eye at a routine follow up visit following injection clinic. Five of these were 3 months after the last full exam with OCT and 1 was 5 months from the last exam with OCT.

**Conclusions:** An injection only clinic may provide a reasonable approach to streamline retina practices.
Diagnoses on urgent visits

**Commercial Relationships:**
- Elizabeth Atchison, None;
- Sophie J. Bakri, San Bio (C), Genentech (C), Regeneron (C), Vindico (C), Valeant (C), Allergan (C);
- Ahmed F. Omar, San Bio (C), Genentech (C), Regeneron (C), None;
- Elizabeth Atchison, None;
- Darren Shu Jeng Ting, Javid Suleman, Philip S. Severn, Sreekumari Pushpoth, The James Cook University Hospital, Middlesbrough, United Kingdom.

**Program Number:** 3348 Poster Board Number: D0151

**Presentation Time:** 8:30 AM–10:15 AM

**Efficacy of aflibercept in wet age-related macular degeneration non-responsive to ranibizumab**

Darren Shu Jeng Ting, Javid Suleman, Philip S. Severn, Sreekumari Pushpoth, The James Cook University Hospital, Middlesbrough, United Kingdom.

**Purpose:** To examine the efficacy of intravitreal aflibercept (Eylea) in patients with wet age-related macular degeneration (AMD) that were previously non-responsive to intravitreal ranibizumab (Lucentis).

**Methods:** This was a retrospective, non-comparative, interventional case series. All cases of wet AMD that were previously non-responsive to intravitreal ranibizumab and required switching to intravitreal aflibercept between July 2013 and November 2014 were included in this study.

**Results:** During the study period, a total of 90 patients were included. The mean age was 75.5 ± 7.3 years with a female preponderance (64%). The mean follow-up period was 11.8 ± 6.2 months. An average of 13.9 ± 8.3 intravitreal ranibizumab injections were given before switching to intravitreal aflibercept. The baseline best-corrected visual acuity (BCVA) on first presentation was 60.9 ± 11.6 letters. The BCVA on switching from ranibizumab to aflibercept was 55.6 ± 14.6 letters, with a mean change of -5.8 letters (p<0.001). At 6-month and 12-month post aflibercept, there was a mean change of +1.3 letters (p=0.17) and -0.3 letters (p=0.82). Inactivity of wet AMD was successfully achieved in 40% (36/90) cases at 6-month post-aflibercept and 38% (20/52) cases at 12-month post-aflibercept. The mean baseline central macular thickness (CMT) pre-aflibercept was 343 ± 127 μm. There was a mean change of -85 μm at 6 months (p<0.001) and -75 μm at 12 months (p<0.001). No complication was noted during the study period.

**Conclusions:** Our study demonstrates that aflibercept serves as an effective and safe alternative treatment in wet AMD that was non-responsive to ranibizumab.

**Commercial Relationships:**
- Darren Shu Jeng Ting, None;
- Javid Suleman, None;
- Philip S. Severn, None;
- Sreekumari Pushpoth, None;
Prediction of low and high anti-VEGF treatment requirements during the PRN phase from early OCT images in neovascular age-related macular degeneration

Hrvoje Bogunovic1, Sebastian M. Waldstein1, Amir Sadeghipour2, Thomas Schlegl1, Bianca Gerendas3, Aaron Osborne1, Ursula Schmidt-Erfurth4, 1Christian Doppler Laboratory for Ophthalmic Image Analysis, Department of Ophthalmology, Vienna Reading Center, Vienna, Austria; 2Genentech, Inc, South San Francisco, CA.

Purpose: In anti-VEGF therapy of neovascular AMD, inter-individual treatment requirements are vastly heterogeneous. Tools and biomarkers to predict these individual requirements represent an unmet medical and socioeconomic need. The aim of this study was to predict anti-VEGF injection requirements during the pro re nata (PRN) phase, using a set of OCT images acquired during the loading phase in treatment-naïve patients with neovascular AMD.

Methods: Prospective clinical trial data of 288 evaluable subjects receiving PRN ranibizumab therapy according to protocol specified criteria in the HARBOR study after 3 initial monthly injections were included. SD-OCT images (512x128x1024 voxels, Cirrus, Zeiss) were analyzed at baseline, month 1 and month 2. Quantitative features based on automated segmentation of layers and fluid regions were extracted to describe the retinal microstructure. Fluid segmentations were based on deep learning and layer segmentations using a graph-theoretic approach. Features included inner retina, outer nuclear layer, photoreceptor outer segments with retinal pigment epithelium, and total retinal thickness (TRT) as well as intra- and subretinal fluid (IRF and SRF) volume and area (Figure 1). An ETDRS grid was used to compute regional features. Groups of low and high injection requirements were defined as ≤2 and ≥9 injections between month 3 and month 12, respectively. Random forest classification was used to predict the low and high treatment categories and was evaluated with a ten-fold cross validation.

Results: The number of injections during the PRN phase until month 12 ranged from 0 to 10. 51/288 patients showed low (≤2) and 49/288 patients showed high (≥9) injection requirements. The classification results were evaluated as area under the ROC curve (AUC). Detection of low and high treatment frequency subgroups demonstrated an AUC of 0.67 and 0.70, respectively. Total retinal thickness at the fovea, as well as SRF in the central 3mm area at month 2 were found to be important OCT-derived prediction features.

Conclusions: We proposed and evaluated a methodology to predict low and high anti-VEGF treatment needs from OCT scans taken early during treatment initiation. The results of this pilot study are a promising step toward image-guided prediction of treatment intervals in neovascular AMD therapy.

Consideration of the benefit of additional intravitreal anti-vascular endothelial growth factor injection in polypoidal choroidal vasculopathy patients with chronic subfoveal subretinal fluid

Jeehyun Kim, Yu Cheol Kim, Kwang-Soo Kim. Keimyung University Dongsan Medical Center, Daegu, Korea (the Republic of).

Purpose: To see the benefit of additional intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection in polypoidal choroidal vasculopathy (PCV) patients with no intraretinal edema at macular area, but with chronic and persisting subfoveal subretinal fluid (SRF) in spite of continuous anti-VEGF injections.

Methods: Study eyes were identified from a consecutive series of 195 PCV patients being treated with intravitreal anti-VEGF therapy by pro re nata protocol for over 1 year of regular follow-up. The clinical histories of 25 eyes of 25 patients with PCV with chronic subfoveal SRF (thickness less than 150 μm) despite appropriate anti-VEGF therapy for over 6 months and without any intraretinal edema at macular area were reviewed. Demographic factors, baseline and
final visual acuity, type and number of anti-VEGF injection, baseline and final thickness of subfoveal choroid and foveal sensory retina, and duration of persistent subfoveal SRF were analyzed.

**Results:** The mean age of patients was 72.3 years. The mean duration of treatment was 45.7 months and the mean duration of persistent subfoveal fluid was 17.3 months. During subfoveal fluid persist, mean best corrected visual acuity of with or without anti-VEGF injection was compared and showed no difference in 20 eyes. Thicker the sensory retina correlated better with final visual acuity (p=0.002). The mean number of injections was 5.2. The thickness of the sensory retina of fovea and subfoveal choroid was not correlated with the number of injection, but both showed significant decrease compared to the thickness before the injection treatment.

**Conclusions:** In eyes with PCV associated with chronic persistent subfoveal SRF despite continuous intravitreal anti-VEGF injection, if the fluid is not thick enough to affect on the visual acuity, the existence may not be the problem and the response to the anti-VEGF injection can be poor. The complication of anti-VEGF injection should be considered and our hypothesis is that the injection may not be much beneficial in those eyes. The prognosis of final visual acuity maybe affected by the final thickness of sensory retina of fovea.

| Table 1: Patient Demographics and Clinical Characteristics |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Inclusion/Exclusion Criteria | Eyes Included | Eyes Excluded | Reason for Exclusion | Baseline Best Corrected Visual Acuity | Final Best Corrected Visual Acuity | Mean Number of Injections | Mean Duration of Persistent Subfoveal Fluid |
| 1 M | 85 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 2 F | 76 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 3 M | 68 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 4 F | 64 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 5 M | 73 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 6 F | 74 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 7 M | 76 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 8 M | 68 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 9 F | 74 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 10 M | 78 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 11 M | 71 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 12 F | 73 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 13 M | 73 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 14 M | 69 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 15 F | 88 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 16 M | 78 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 17 M | 86 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 18 M | 78 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 19 M | 67 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 20 M | 68 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 21 F | 76 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 22 F | 78 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 23 M | 78 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 24 M | 74 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |
| 25 F | 81 | 2 | 1 missing study visit, which was ≤ 5-letter decrease in BCVA from the previous visit | 20 | 17.3 | 5.2 | 12.5 |

Table 1: Patient Demographics and Clinical Characteristics

**Figure 1:** The Relationship Between the Final Thickness of Foveal Sensory Retina and the Final Snellen Acuity

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Retinal angiomatous Proliferations - does the treatment outcome depend on the stage? A retrospective follow-up

**Johanna Maass.** Ophthalmology, Universitätsklinikum Carl Gustav Carus, Dresden, Germany.

**Purpose:** Retinal angiomatous proliferations (RAP) are classified as a subtype of neovascular age related macula degenerations (nAMD). The prevalence of RAP lesions is 10-15% in Caucasians and 5% in Asians. RAP lesions are categorized in three stages with a subdivision in IIA and IIB. The treatment of RAP with Anti-VEGF agents has often been described as not as successful as in other types of nAMD. Our aim was to find out whether treatment outcome with Ranibizumab differed among the three stages of RAP.

**Methods:** 36 patients with diagnosed retinal angiomatous proliferation were evaluated. Best corrected visual acuity (BCVA) was obtained before, during and after upload with Ranibizumab. Data among the four stages (with specification in IIA and IIB) were compared.

**Results:** RAP lesions in stage I and IIA responded better to treatment than later stages. RAP type I had a gain of 2.0 lines (1st injection 0 lines, 2nd + 3rd injection +0.80 lines), RAP type IIA and type IIB lost 0.21 lines (1st injection: +0.75 lines, 2nd injection: -0.46 lines, 3rd injection: +0.29 lines) and 0.90 lines (1st injection: +0.22 lines, 2nd injection: -0.49 lines, 3rd injection: +0.33 lines) respectively and RAP type III lost 1.12 lines (1st injection: -0.05 lines, 2nd injection: -0.33 lines, 3rd injection: -0.26 lines) after 3 injections.

**Conclusions:** RAP lesions regardless of stage do not respond well to treatment. Earlier types of RAP seem to have a better outcome than late stages, which appear to result in a poor treatment outcome. Consequently patients suffering from this special subtype profit from an early identification and an early treatment.

**Commercial Relationships:** Johanna Maass, None

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Time to recurrence in neovascular age-related macular degeneration after ranibizumab treatment: baseline characteristics of treatment-naïve patients enrolled in the ORACLE study

**François Devin**, Eric Fournaux, Gabriel Quentel, Joel Uzzan, Maddalena QUARANTA EL-MAFTOUHI, Catherine François-Maury, Wilfried Roquet, Laurent Castelnovo, Sam Razavi, Laetitia Finzi. Ophthalmology, Palais Galien, Bordeaux, France; 
*2Centre Imagerie et Laser, Paris, France; 3Ophthalmology, Clinique Mathilde, Rouen, France; 4Ophthalmology, Centre Rabelais, Lyon, France; 5Ophthalmology, Centre de l’Océan, Paris, France; 6Ophthalmology, Centre Blatin, Clermont-Ferrand, France; 7Ophthalmology, Clinique Saint-Gatien, Tours, France; 8Retine, Novartis Pharma SAS, Rueil-Malmaison, France; 9Ophthalmology, Centre Monticelli Paradis, Marseille, France; 10Ophthalmology, Clinique Maison Rouge, Strasbourg, France.

**Purpose:** Attempts have been made to individualize ranibizumab treatment using pro re nata and treat-and-extend regimens to fit therapeutic procedures to the rhythm of recurrences of choroidal neovascularization (CNV). The ability to predict the recurrence interval for an individual patient would help in making retreatment decisions in wet age-related macular degeneration (wAMD).

**ORACLE** is an ongoing 24-month, multicenter, observational study, designed to evaluate the time to recurrence of disease activity in newly diagnosed wAMD patients treated with ranibizumab over 2 years. Here we present baseline characteristics of the enrolled population.

**Methods:** Patients were enrolled at 69 centers across France between March 2014 and July 2015. Consenting adult patients aged ≥ 55 years with treatment-naïve and active subfoveal CNV were included. The decision to retreat was at the investigator’s discretion. The key endpoints of the study are summarized in Table 1.

**Results:** Of the 746 patients screened, 706 were enrolled into the study. The mean age (± SD) of patients was 80.2 (± 7.4) years, 66.9% were females and 26.1% had bilateral disease. The mean (± SD) time between diagnosis and initiation of the treatment was 3.16 (± 47.3) days. In the majority of patients, the CNV subtype was categorized as occult (52.6%) followed by predominantly classic (32.9%) and classic (14.5%). For the study eye, the mean best corrected visual acuity at baseline was 58.0 (± 16.9) letters and the mean central retinal thickness was 362.1 (± 115) μm. Other baseline ocular characteristics are presented in Table 2. On optical coherence tomographic (OCT) scans, 48.2% (n = 340) patients had Pigment Epithelial Detachments (PED) at baseline with a mean PED height of 218.7 μm (n = 225).

**Conclusions:** The overall baseline characteristics of the study cohort give insight on the demographics, functional and anatomical parameters of treatment-naïve patients with wAMD. These epidemiological data from the ORACLE study will help to better define the profile of wAMD patients initiating ranibizumab in 2015. This study will further provide data to better predict the need for retreatment with ranibizumab in wAMD.

![Table 1: Key endpoints of the ORACLE study](image-url)
Table 2: Other baseline ocular characteristics of wAMD patients in the ORACLE study

Commercial Relationships: François Devin, Thea (C), Novartis (C), Roche (C), Zeiss (C), Bayer (C), Allergan (C), Ophthotec (C); Eric Fournaux, Novartis (C); gabriel quentel, Novartis (C), Alimera (C), Zeiss (C), Bayer (C); Joel Uzzan, Novartis (C); Maddalena QUARANTA EL-MAFTOUHI, Novartis (C); Catherine Francais-Maury, Novartis (C); Wilfried Roquet, Novartis (C); Laurent Castelnovo, Novartis (C); Sam Razavi, Novartis (C), Bayer (C); Laetitia Finzi, Novartis (C)

Support: Novartis Pharma SAS

Program Number: 3355 Poster Board Number: D0157
Presentation Time: 8:30 AM–10:15 AM

An overview of medical practices in neovascular age-related macular degeneration: evaluating the changes in France between 2013 and 2016

Nathalie San Nicolas1, Vincent Gualino2, Jennifer Zerbib1, Typhaine Grenet1, Maté Streho1, Jeremy Halfon2, Pierre -Louis Cornut1, Alexandre Bourhis1, Camille Maurin3, Helene Masse4. 1Novartis Pharma SAS, Rueil-Malmaison, France; 2Ophthalmology, Centre Honoré Cave, Montauban, France; 3Ophthalmology, Private practice, Nice, France; 4Centre Imagerie et Laser, Paris, France; 5Centre Exploration de la Vision, Rueil-Malmaison, France; 6Cabinet D’ophthalmologie des Halles de Tours, Tours, France; 7Pôle Vision, Clinique Du Val d’Ouest, Lyon, France; 8Ophthalmology, Polyclinique de L’Atlantique, Saint-Herblain, France; 9Ophthalmology, Chu Nantes, Nantes, France.

Purpose: The LYVE survey employed a unique design that used two databases in France to evaluate the frequency of ranibizumab (RBZ) and aflibercept (AFL) deliveries over the 12-month follow-up period for treatment-naive patients with neovascular age-related macular degeneration (nAMD) in routine medical practice.

Methods: A quantitative internet survey among 150 ophthalmologists in France (general ophthalmologists, 90; retinal specialists, 60) will be conducted in January 2016. Quantitative questions are developed by a committee of experts. Most questions are similar to those included in the 2013 and 2015 surveys. These questions evaluate: i) diagnosis, treatment, and follow-up parameters, ii) logistical organization and access to care for nAMD patients, and iii) current treatment protocols.

Results: Data from the 2013 and 2015 surveys showed that treatment regimens used by retinal specialists are highly variable. However, the treat and extend (T&E) regimen was more popular in 2015 compared with 2013 (17% vs 4%). In the 2013 survey, the effectiveness of the treatment initiation phase was assessed using optical coherence tomography (OCT) in 70% of the cases and visual acuity (VA) test in 100% of the cases; in 2015, it was assessed using OCT in 99% of the cases and the VA test in 89% of the cases. In comparison with these data, the results of the 2016 survey will show if the management of nAMD has changed from 2013 through 2016.

Conclusions: Comparison of the results from the 2013, 2015, and 2016 surveys will provide new insights on the management of nAMD patients in France. The 2016 results are expected in March 2016.

Commercial Relationships: Nathalie San Nicolas, Novartis Pharma SAS; Vincent Gualino, Novartis (C), Bayer (C), Alcon (C), Allergan (C); Jennifer Zerbib, Novartis (C); Typhaine Grenet, Novartis (C), Bayer (C), Allergan (C); Maté Streho, Novartis (C), Bayer (C), Allergan (C); Jeremy Halfon, Novartis (C); Pierre-Louis Cornut, None; Alexandre Bourhis, Novartis (C); Camille Maurin, Novartis Pharma SAS; Helene Masse, Novartis (C)

Support: Novartis Pharma SAS

Program Number: 3355 Poster Board Number: D0158
Presentation Time: 8:30 AM–10:15 AM

Efficacy of Aflibercept in Treatment-naive Neovascular Age-related Macular Degeneration: Two-Year Real World Outcomes


Purpose: To report 2 year, real-world visual and anatomical outcomes of aflibercept (Eylea® Bayer Pharma, Germany) treatment in patients with neovascular AMD (nAMD).

Methods: We performed a retrospective, observational study analysing 2-year treatment outcomes of aflibercept intravitreal injections in consecutively treated, treatment naïve eyes with nAMD in patients from all Moorfields Eye Hospital sites. Consecutive patients from October to December 2013, with 24±1 months follow up were included. Treatment was started following NICE (National Institute for Health and Care Excellence) guidance for funding treatment, which included best-corrected visual acuity (BCVA) between 24 and 73 ETDRS letters. Key exclusion criteria were: ≤ 15 ETDRS letters in year 1, ungradable OCT images, absence of OCT at baseline or final visit and concomitant ocular conditions affecting BCVA or macular anatomy. Aflibercept was administrated 2 monthly for the first year after 3 initial monthly injections, and in a treat and extend regimen for the second year. The primary outcome was the percentage of patients who maintained visual acuity (loss of ≤ 15 ETDRS letters from baseline) at 2 years. Secondary outcomes included mean change in BCVA, change in central macular thickness (CMT), gain of ≥ 15 letters and percentage of patients with signs of active disease (macular fluid) on OCT imaging, determined by single grader at 2 years.

Results: Of 129 patients, 43 eyes of 43 patients (33.3%) satisfied the inclusion criteria, with incomplete follow-up (n=35, 40.7%) the key reason for exclusion. At 1 year, 88.4% of patients maintained visual acuity with a mean gain in VA of 8.7±16.4 letters and a mean reduction in CMT of 102.9±102.5µm. 47.5% had active disease in the OCT at year 1. At 2 years, 90.7% of patients maintained visual acuity, with an average of 12.3 (±8.3) injections. The mean gain in VA was 7.8 ±16.1 letters with a mean reduction in CMT of 103.0 ±115.0 µm at 2 years. 25.6% gained a minimum of 15 letters. 27.9% showed signs of active disease on OCT imaging at the end of 2 year follow-up.

Conclusions: Aflibercept use for nAMD in routine clinical practice resulted in comparable visual outcomes after 2 years to outcomes

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seen in the 96 week extension phase results from the VIEW clinical trials.

**Commercial Relationships:** Maria Eleftheriadou, None; Clara Vázquez-Alfageme, Maria C. Citu, None; Roxanne R. Crosby-Nwaobi, None; Sohba Sivaprasad, Novartis (C), Bayer (C), Roche (F), Allergan (C), Bayer (F), Allergan (F), Novartis (F); Philip Hykin, Novartis (C), Bayer (C), Allergan (C), Bayer (F), Novartis (F); Robin D. Hamilton, Novartis (C), Ellex (R), Novartis (R), Bayer (C), Bayer (R), Novartis (F), Ellex (C), Allergan (R), Bayer (F), Allergan (C); Praveen J. Patel, Salutaris MD (R), Novartis (C), Thrombogenics NV (C), Heidelberg Inc (F), Topcon Inc (F), Thrombogenics NV (F), Bayer (C)

**Program Number:** 3356 **Poster Board Number:** D0159

**Presentation Time:** 8:30 AM – 10:15 AM

**Recurrences in neovascular age related macular degeneration: are they predictable in a clinical setting?**

Stefano Erba, Giulia Delledonne, Carlo D. Bianchi, Mariano Cozzi, Alessandro Babbì, Mario V. Cigada, Ferdinando Bottoni, Giovanni Staurenghi. Biomedical and clinical sciences “Luigi Sacco”, Sacco Hospital Eye Clinic, University of Milan, Milano, Italy.

**Purpose:** To evaluate the first recurrence in naive neovascular AMD after three loading doses of Ranibizumab and to assess the risk of subsequent recurrence through retrospective review.

**Methods:** Design of the study: retrospective review. 93 eyes (87 patients) with naïve CNV (occult-type 1 n=46, classic-type 2 n=23, Retinal Angiomatics Proliferation (RAP)-type 3 n=19 and polyoidal choroidal vasculopathy (PCV) n=5) with no sign of activity (e.g. any intra-, sub-retinal fluid on SD-OCT, new hemorrhage, reduction in visual acuity attributable to neovascular AMD or leakage on fluorescein angiography) after the three loading doses of ranibizumab were enrolled. Only patients with a follow up of 30-45 days between every visit for at least 1 year were included. Recurrences were retreated in pro re nata (PRN) regimen. Exclusion criteria included any previous ophthalmic surgery, except for cataract removal. Eyes with any previous treatment for neovascular AMD (e.g. focal laser, photodynamic therapy, other type of anti-VEGF drugs) were excluded. Survival for the first recurrence was estimated by Kaplan-Meier analysis. Coefficient of variation of the mean recurrence interval was calculated for every patient.

**Results:** The mean age of patients was 79 years (range 62-91). Mean follow up time was 978 days (range 476-1725). Kaplan Meier analysis showed that the 50% (CI 40%-60%) of neovascular lesions showed signs of reactivation by the forth month (120 days) after the third injection. Subgroup analysis showed that 50% type 3 lesions reactivated by the day 107, type 1 by the day 126, type 2 by the day 175 and PCV by the day 217. Coefficient of variation of the mean recurrence interval was 0,52, interquartile range (IQR) 0,33-0,63.

**Conclusions:** Although this is a small cohort of patients with neovascular AMD, our data suggest a clear trend in the first recurrence. RAP-type 3 showed recurrence earlier than occult-type 1 or classic-type 2 lesions. PCV lesions, although a small sample in this cohort, showed a larger interval for the first recurrence. These data may be used to plan a tailored follow up visit after the three loading doses of ranibizumab. Coefficient of variation of the mean recurrence interval showed large intra-individual fluctuations. Recurrences of the neovascular lesions cannot be predicted only on the basis of the first year of follow up.

**Commercial Relationships:** Stefano Erba, None; Giulia Delledonne, None; Carlo D. Bianchi, None; Mariano Cozzi, Bayer AG (F), Heidelberg Engineering (F), Alcon (F); Alessandro Babbì, None; Mario V. Cigada, None; Ferdinando Bottoni; Giovanni Staurenghi, Bayer AG (F), QLT (C), Bayer AG (C), OD-OS (C), Allergan (F), Alcon (C), GSK (C), Quantel Medical (F), Carl Zeiss Meditec (C), Ocular Instruments (P), Heidelberg Engineering (F), Novartis (C), Optos (C), Roche (C), Heidelberg Engineering (C), Quantel Medical (C), Genentech (C), Alcon (C), Boheringer (C), Allergan (C)

**Program Number:** 3357 **Poster Board Number:** D0160

**Presentation Time:** 8:30 AM – 10:15 AM

**Fc receptor inhibition reduces susceptibility to oxidative stress in human RPE cells treated with bevacizumab, but not aflibercept**

Mahdy Ranjbar, Max Philipp Brinkmann, Dorinija Zapf, Yoko Miura, Martin Rudolf, Salvatore Grisanti. Ophthalmology, University of Lübeck, Lübeck, Germany.

**Purpose:** Anti-vascular endothelial growth factor (VEGF) drugs like aflibercept and bevacizumab have shown to be most effective in treating neovascular age-related macular degeneration (AMD). VEGF-A is induced by oxidative stress, and functions as a survival factor for various cell types, including retinal pigment epithelial (RPE) cells. Uptake of the aforementioned drugs into the RPE has already been shown, with involvement of the Fc receptor (FcR) being assumed, but not demonstrated yet. Herein, we evaluated the significance of the FcR within this context.

**Methods:** RPE cells were treated with aflibercept and bevacizumab in presence or absence of H2O2 as oxidative stress stimulus. After 24h cells were evaluated for drug uptake, VEGF-A expression and secretion, levels of intracellular reactive oxygen species (ROS) as well as cell proliferation. Experiments were repeated with cells being pre-incubated with an FcR inhibitor prior to drug application.

**Results:** As expected, aflibercept and bevacizumab inhibited extracellular levels of VEGF-A and were also taken up into the RPE cells. Furthermore, intracellular levels of VEGF-A were significantly reduced. When oxidative stress was applied, intracellular ROS levels in cells treated with aflibercept and bevacizumab rose, and cell proliferation was reduced. Prior incubation with the FcR inhibitor lessened the uptake of bevacizumab, but not aflibercept into RPE cells, and simultaneously enhanced cell survival under oxidative stress conditions.

**Conclusions:** Our results indicate that uptake and accumulation of aflibercept and bevacizumab within RPE cells affects the intracellular VEGF-A metabolism negatively leading to a biologically relevant reduced cell survival under oxidative stress. The FcR plays a substantial role in the uptake of bevacizumab, but not aflibercept, which allows an enhanced RPE cell survival through FcR blockade in an environment dominated by oxidative stress, as clinically significant for various inflammatory retinal disorders.

**Commercial Relationships:** Mahdy Ranjbar, None; Max Philipp Brinkmann, None; Dorinija Zapf, None; Yoko Miura, None; Martin Rudolf, None; Salvatore Grisanti, None

**Program Number:** 3358 **Poster Board Number:** D0161

**Presentation Time:** 8:30 AM – 10:15 AM

**Comparative Effects of Bevacizumab and Aflibercept on VEGF and IGF Signaling in Human Retinal Endothelial Cells Exposed to Hyperoxia and Intermittent Hypoxia**


**Purpose:** Vascular endothelial growth factor (VEGF) inhibitors are mainstays of treatment in retinal vasculature abnormalities in adults and in part, in premature infants. Bevacizumab (Avastin) has long been used and studied in various clinical scenarios; however, literature is naïve with respect to the safety and efficacy of newer
anti-VEGF agents such as Aflibercept (Eylea). Here we examined and compared the effects of Avastin and Eylea on VEGF and IGF-I signaling pathway in human retinal endothelial cells (HREC) exposed to hyperoxia, intermittent hypoxia (IH) and normoxia (Nx)

**Methods:** HREC were treated with Avastin (0.2 µg/mL); low-dose Aflibercept (Lo-AFC, 0.2 µg/mL); or high-dose Aflibercept (Hi-AFC, 0.4 µg/mL) and exposed to normoxia (Nx), hyperoxia (50% O₂), or IH (50% O₂ with 10% O₂, 8 IH episodes/day) for 24, 48 or 72 hrs. VEGF (pg/mL), sVEGFR-1 (pg/mL), IGF-I (ng/mL) levels were determined in the media. Cells were stained for HIF-α, VEGF, IGF-I, and soluble VEGF (sVEGFR) and IGF receptors. Lipid peroxidation, and cell migration and tube-forming capacities were also determined.

**Results:** At any given time point, Eylea was superior to Avastin for suppression of VEGF and thus, significantly increased sVEGFR-1, the endogenous VEGF trap. However, at 72 h time point, higher expression of receptors were detected in the Avastin treated cells which is most likely due to the shorter half-life of Avastin. Additionally, Eylea treated cells under IH expressed highest levels of sVEGFR-1 as opposed to other oxygen conditions in the same group or Avastin treated group. Surprisingly, the IGF-1 levels in the Avastin group were low, while levels in the Eylea treated group were significantly higher across different time points or oxygen conditions, and correlated with sVEGFR-1 levels. Under IH, Avastin decreased migration and tube formation more effectively than Eylea, however in normoxia the effect was opposite. Both Avastin and Eylea induced lipid peroxidation, but the effect was more substantial in the Eylea group under IH.

**Conclusions:** Eylea appears to have a more rapid and predominant suppressive effect on VEGF than Avastin. The metabolic effect of both drugs on HREC’s seems to be diverse based on the oxygen environment. The effects of Eylea are highly potentiated by IH. Further investigation of the long term safety profile of both drugs is warranted.

**Commercial Relationships:** Amirfarbod Yazdanyar, None;
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**Support:** NICHD #1U54HD071594

**Program Number:** 3359 Post Board Number: D0162
**Presentation Time:** 8:30 AM–10:15 AM

### No improvement in visual outcome over time in two cohorts from the same county in patients treated for wet AMD

**Marion Schroeder, Lena Rung, Monica K. Lovestam Adrian.** Lund University, Malmö, Sweden.

**Purpose:** Treatment with ranibizumab has been in use for treatment of wet AMD (age-related macular degeneration) since 2007. Previous studies have reported undertreatment and less favourable visual outcome. In this study we evaluated two cohorts of patients with AMD before intravitreal treatment with ranibizumab and at four-year respectively three-year follow-up. The main focus was laid on visual outcome and quality of life (QoL) status.

**Methods:** We compared patients with treatment-naive wet AMD in two follow-up cohorts 2007-2010 (n=55 patients) and 2009-2013 (n=26). After a loading dose of three intravitreal ranibizumab injections patients were treated under Pro Re Nata (PRN) regimen. We examined best corrected visual acuity (VA) by using Early Treatment Diabetic Research Study (ETDRS) charts and evaluated the Visual Function Questionnaire (NEI VFQ-25) at baseline with 37 ± 7 months (cohort 1) follow-up 45 ± 4 months (cohort 2).

**Results:** At baseline the cohorts were homogeneous considering mean age (75 ± 7 vs. 75 ± 8 years), mean VA (53 vs. 52 letters) and mean self reported duration (14 ± 11 vs. 13 ± 11 weeks). Mean VA decreased in both cohorts over time; 53 ± 14 to 45 ± 24 letters (p = .011) and 52 ± 15 to 46 ± 22 (p = .175) respectively. The patients received mean 8 ± 5 and 9 ± 7 injections respectively. In spite of deterioration of VA, life quality test demonstrated only a decrease in social functioning 75 ± 27 to 65 ± 30 scores (p = .029) and role limitations 67 ± 29 to 56 ± 32 scores (p = .034) in cohort 1.

**Conclusions:** Although treatment with intravitreal injections is the standard care for wet AMD since many years, no improvement was seen in frequency of injections and visual outcome over years in two different clinical cohorts from the same county in Sweden.

**Commercial Relationships:** Marion Schroeder: Lena Rung, None; Monica K. Lovestam Adrian, None

**Program Number:** 3360 Poster Board Number: D0163
**Presentation Time:** 8:30 AM–10:15 AM

### Impact of practice modifications on infectious endophthalmitis rates following intravitreal injection of anti-vascular endothelial growth factor

**Maya Maloney, Andrew Barkmeier, Sophie J. Bakri, Raymond Iezzi, Jose Pulido, Wendy Smith, Jay Erie.** Mayo Clinic, Rochester, MN.

**Purpose:** To assess the effectiveness of practice modifications in reducing infectious endophthalmitis rates among patients undergoing intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF).

**Methods:** A retrospective review of all cases of clinically suspected endophthalmitis after intravitreal injection of anti-VEGF from January 2011 through September 2015 was performed. In May 2013, practice modifications to the intravitreal injection practice were implemented and included the mandatory use of masks by nurses and physicians while in injection rooms, conversion to a sterile instrument tray setup, room cleaning between all patients by using Oxivir TB disinfectant wipes (Diversey, Inc., Sturtevant, WI), and converting injections from an office-based setting to an outpatient surgery center setting. Chi-square testing was used to compare endophthalmitis rates before and after implementation of practice changes.

**Results:** Before practice modifications, 9 cases of clinically suspected endophthalmitis were identified after a total of 17,008 injections (0.05%; January 1, 2011 through April 30, 2013). Following implementation of practice modifications, 2 cases of endophthalmitis was identified after 24,229 injections (0.008%; P=0.009; May 1, 2013 through September 30, 2015).

**Conclusions:** Post-intravitreal injection endophthalmitis rate was significantly reduced following practice modifications that included the use of masks by nurses and physicians, conversion to a sterile instrument tray setup, room cleaning between all patients, and converting injections to an outpatient surgery center setting. It is unclear which of these modifications, if any, are responsible for the decrease in endophthalmitis rates.

**Commercial Relationships:** Maya Maloney; Andrew Barkmeier, None; Sophie J. Bakri, Allergan (C); Raymond Iezzi, Alcon (C); Jose Pulido, None; Wendy Smith, None; Jay Erie, None

**Program Number:** 3361 Poster Board Number: D0164
**Presentation Time:** 8:30 AM–10:15 AM

### Suppression of laser-induced choroidal neovascularization by intravitreal injection of collagen type II, alpha 1 peptide in mouse model

**Byul-Nim Ahn, Dae Young Hur, JaeWook Yang, Si-Kyung Kim.** Inje Univ. Busan Paik hospital, Busan, Korea (the Republic of).

**Purpose:** To investigate the effect of collagen type II, alpha1 peptide (G-Q-D-G-L-A-G-P-K) on experimental choroidal neovascularization (CNV) and human umbilical vein endothelial cell tube formation.

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Methods: Tube formation was assayed in VEGF induced Ea.hy-926 cell cultures in matrigel. CNV was induced in C57BL/6 mice by laser photoagulation (4 spots per eye, 532 nm, 240 mW, 0.1 sec duration, 50 μm spot size). Mice were divided into four groups: control group (intravitreal injection of PBS only, n=5), CNV group (laser and PBS injection, n=10), positive control group (laser and 5 μg of avastin injection, n=10) and CPII group (laser and 5 μg of CPII injection, n=10). Intravitreal injections of avastin and CPII were performed for 5 days starting at day of laser injury. Two week after laser treatment, size of CNV was quantified by retina/choroid flat mounts labeled with 25 mg/ml fluorescein isothiocyanate (FITC)-dextran. The angiogenic factors expression in retina/choroid complex were determined by western blot analysis.

Results: CPII at the concentration of 200 μg/ml decreased the number of newly formed capillary tubes in response to vascular endothelial growth factor. Two weeks after laser photoagulation, Intravitreal injection of CPII significantly decreased the size of the CNV lesions compared with vehicle (PBS) injections. The expression levels of vascular endothelial growth factor, VEGFR-1, -2 and angiopoietin 2 in retina/choroid complex were increased after laser photoagulation. However, the expression of these angiogenic factors were suppressed by collagen type II, α1 peptide.

Conclusions: Collagen type II, α1 peptide demonstrated antiangiogenic properties in human umbilical vein endothelial cell and mouse model of CNV. Therefore, CPII is possible promising material for treatment of choroidal neovascularization.

Commercial Relationships: Byun-Nim Ahn, None; Dae Young Hur, None; JaeWook Yang, None; Si-Kyung Kim, None
Support: This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare Affairs, Republic of Korea (grant #: HI12C0005)

Program Number: 3362 Poster Board Number: D0165
Presentation Time: 8:30 AM–10:15 AM

Adherence to treatment determines 5-year outcome in neovascular AMD in a real-life setting
Robert G. Wilke, Helmut G. Sachs. KH Dresden - Friedrichstadt, Dresden, Germany.

Purpose: We were interested in understanding which factors determine relatively poor 5-years outcome of anti-VEGF treatment of AMD in a real-life setting as compared to prospective studies. We investigated if there is a subpopulation in our real-life data that has a significantly better 5-years outcome by stratifying by disease stages, number of injections, access to treatment and adherence to treatment.

Methods: This is a retrospective analysis of 1500 cases of neovascular AMD being treated according to a PRN scheme between 2010 and 2014. Letter scores for a period of up to 5 years have been evaluated as well as number of injection in each year. Visual acuity at baseline served as a marker for disease stage at baseline, the interval between visits as a marker for adherence to therapy. At a certain time access to treatment was greatly facilitated by introducing a general treatment allowance for the public healthcare system. Accordingly, subgroups have been defined as earlier disease stages, higher number of injections, faster access to treatment and adherence to treatment.

Results: In the overall population the initial gain in letter score is reverted by end of year 2. The subgroups with high injections and earlier disease stages have both a significantly better outcome, however by year 3 there is also a loss below baseline. Ease of access to treatment clearly improves the initial gain, where a second upturn in letter score after the initial upload is observed. Only the group with good adherence to treatment, however, continues to have a positive letter score over 5 years.

Conclusions: More than the stage of disease do adherence to treatment and access to treatment determine long term outcome in anti-VEGF treatment in AMD in a PRN setting.

Commercial Relationships: Robert G. Wilke, Novartis Pharma GmbH (R); Helmut G. Sachs, None
Support: supported with a grant by Novartis Pharma GmbH

Program Number: 3363 Poster Board Number: D0166
Presentation Time: 8:30 AM–10:15 AM

Ranibizumab, Bevacizumab, and Aflibercept accumulation and their effect on cell migration and permeability on human ARPE-19 cells
Patricia Fernandez1, 2, Manuel Saenz de Viteri1, Sergio Recalde1, 2, Maria Hernandez1, 2, Iaione Bezuinartea-Bezuinartea1, 2, Elena Alonso1, Maite Moreno-Orduna1, Natalia Aguado1, Idoia Belza1, Alfredo Garcia-Layana1, 2, 1Experimental Ophthalmology Laboratory, Clinica Universidad de Navarra, Pamplona, Spain; 2IdiSNA, Navarra Institute for Health Research, Pamplona, Spain.

Purpose: To evaluate intracellular accumulation and the effect of bevacizumab, ranibizumab and aflibercept on cellular migration and permeability in a human retinal pigmented epithelium (RPE) cell line.

Methods: Experiments were performed on ARPE-19 cells and anti-VEGF drugs were diluted to a concentration equivalent to their clinical doses. Anti-VEGFs were labeled with Alexa 488 fluorochrome to detect intracellular accumulation by flow cytometry at 1 hour, 1 day and five days. Further, transepithelial electrical resistance (TEER) was measured in tranwells at 2, 4, 6, 12 and 24 hours to assess the effect of anti-VEGFs on RPE permeability. Moreover, TEER was also measured at the same time points in the presence of different doses of H2O2 to replicate the oxidative environment observed in Age-related Macular Degeneration (AMD). Wound healing was assessed to determine the effect of the drugs on cellular migration during 72 hours to measured cell covered area by Imaged software.

Results: The three studied drugs were observed to accumulate inside the cells and they were still detectable five days after being added (p<0.001). A dose-dependent increase in cell permeability was observed in cells treated with H2O2 (p<0.05) that was reverted from the time point of 12 hours and became non-significant. Anti-VEGF drugs did not affect the permeability along time and they were able to reduce the effect of H2O2 at 4, 6 and 12 hours (p<0.05) with no significant difference between the treatments. On the contrary, when anti-VEGF treatment was used 6 hours after the beginning of the experiment, none of the 3 drugs decreased the deleterious effect of H2O2 in TEER. Anti-VEGF drugs did not affect cellular migration.

Conclusions: Intracellular accumulation of bevacizumab, ranibizumab and aflibercept does not seem to be toxic or affect cell permeability and migration. Moreover, our study suggests that anti-VEGF drugs have a positive effect on the barrier function of the RPE.

Commercial Relationships: Patricia Fernandez, Manuel Saenz de Viteri, None; Sergio Recalde, None; Maria Hernandez, None; Iaione Bezuinartea-Bezuinartea, None; Elena Alonso, None; Maite Moreno-Orduna, None; Natalia Aguado, None; Idoia Belza, None; Alfredo Garcia-Layana, Novartis (C), Thea Laboratoires (C), Bayer (C), Allergan (C), Alcon (C)
Clinical outcomes of treatment switching in neovascular age-related macular degeneration (nAMD): A retrospective cohort study in the United States (US) using electronic medical records

Frances Milnes¹, Raymond Griner², Alberto Ferreira³, Adrian Skelly⁴, Pravin U. Dugel⁵.

¹Novartis Pharma AG, Basel, Switzerland; ²IMS Health Inc., Burlington, MA; ³Novartis Ireland Limited, Dublin, Ireland; ⁴Retinal Consultants of Arizona, Phoenix, AZ.

Purpose: To compare best corrected visual acuity (BCVA letter score) outcomes in nAMD pre- and post-ranibizumab and aflibercept treatment switch in a real-world setting.

Methods: Data were extracted from 53 retina practices across the US using a standardized electronic medical record system. Treatment-naïve eyes were included if they had a nAMD diagnosis, a first ranibizumab or aflibercept injection between July 2011 and July 2014, at least one record of switch treatment and a BCVA reading at Month 12 (M12) post-switch. Eyes were excluded if they discontinued index treatment (>180 days with no treatment or BCVA ≤69 letters) prior to receipt of switch treatment. The primary outcome was the mean (±standard deviation [SD]) change in BCVA from switch to M12. Treatments were compared using ANCOVA adjusted for BCVA at switch and study drug. Mean BCVA change prior to switch was also assessed. A non-inferiority margin of 5 letters was set. Both aflibercept and ranibizumab provided a comparable change in BCVA at 12 months post-switch.

Results: The initial mean PCT of PCV (153.78 ± 56.23 μm) was thicker than that of exudative AMD (88.77 ± 23.11 μm, P < 0.001). Temporal, superior, nasal, and inferior PCT of PCV were all thicker than exudative AMD (all, P < 0.05). After anti-VEGF, the mean PCT of PCV was significantly reduced (134.17 ± 41.66 μm, P < 0.001) but not in exudative AMD (86.87 ± 22.54 μm, P = 0.392). PCT in each quadrant showed a similar trend.

Conclusions: PCV exhibit a thick choroid overall in both the peripapillary and macula regions. Both regions decrease in thickness after anti-VEGF in PCV, but not in exudative AMD. In exudative AMD, subfoveal CT decreased but the peripapillary region did not.

Commercial Relationships: Frances Milnes, Novartis Pharma AG; Raymond Griner, IMS Health Inc.; Alberto Ferreira, Novartis Pharma AG; Adrian Skelly, Novartis Ireland Limited; Pravin U. Dugel, Novartis (C), Genentech (C), Alcon (C)
Conclusions: Given the sensitivity of BP changes and kidney function as a proxy for systemic anti-VEGF activity, the data from 3 large Phase 3 studies indicate the absence of systemic pharmacodynamic effects due to exposure to RBZ or IAI.

Commercial Relationships: Peter K. Kaiser, Bayer Healthcare (C); Laurent Kodjikian, Bayer Healthcare (C); Jean-Francois Korobelnik, Novartis (C), Roche (C), Alcon (C), Horus (C), Thea (C), Alimera (C), Zeiss (C), Allergan (C), Bayer Healthcare (C); Oliver Zeitz, Bayer Pharma AG; Robert Vitti, Regeneron Pharmaceuticals Inc.; Carola Metzig, Bayer Pharma AG; Christiane Ahlers, Bayer Pharma AG; Thomas dicioccio, Regeneron Pharmaceuticals Inc.; Joachim Hoochel

Clinical Trial: NCT00509795

Program Number: 3367 Poster Board Number: D0170
Presentation Time: 8:30 AM–10:15 AM
A systematic review to assess the “Treat-and-Extend” dosing regimen compared to monthly and as-needed dosing for neovascular age-related macular degeneration using ranibizumab Sohaib R. Rufai1, 2, Hussein Almuhtaseb1, Helena Lee1, 2, Richard Paul1, Beth Stuart2, Tony Kendrick2, Andrew J. Lotery1, 2
1Southampton Eye Unit, University Hospital Southampton, Southampton, United Kingdom; 2Faculty of Medicine, University of Southampton, Southampton, United Kingdom.

Purpose: Age related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. Monthly or as-needed (PRN) dosing of intravitreal ranibizumab have been established as efficacious treatment options for neovascular AMD. More recently, the “Treat-and-Extend” dosing regimen (TREX) is increasingly being adopted in clinical practice as it represents a patient-centric and economical option, reducing treatment burden by extending injection intervals when possible. However, the efficacy of TREX remains to be defined. This systematic review aims to evaluate the effectiveness of TREX compared to monthly and PRN ranibizumab dosing.

Methods: A systematic review was performed to assess the current evidence for TREX using MEDLINE, Embase and PubMed. Only studies which included ranibizumab treatment of neovascular AMD using TREX were included. The primary outcome measure was mean change in best-corrected visual acuity (BCVA) at one year, using Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Secondary outcome measures included number of injections at one year.

Results: Of 1,733 studies identified, 11 studies were included in our analysis, consisting of one randomized controlled trial (RCT), three prospective and seven retrospective studies. The RCT demonstrated mean BCVA improvements of 9.2 and 10.5 letters in the monthly and TREX cohorts at one year, respectively (P=0.60). One prospective comparative study demonstrated mean BCVA improvements of 10.8 and 2.3 letters in the TREX and PRN cohorts at one year, respectively (P=0.036). No other studies compared TREX to regular or as-needed dosing. Full data for mean BCVA improvement and mean number of injections were obtained for nine studies comprising 748 eyes. BCVA improvement was 9.00 letters at one year, as a weighted mean accounting for numbers of study eyes; mean number of injections was 7.66 (S.D. 1.89) at one year.

Conclusions: Previously, the landmark ANCHOR and MARINA trials reported gains of 11.3 and 7.2 letters, respectively, using monthly ranibizumab, while the PrONTO trial reported a 9.3 letter gain using PRN ranibizumab (mean of 5.6 injections) at one year. Our analysis suggests that comparable results can be achieved using TREX, but further RCTs are needed to fully evaluate the long-term efficacy and economy of TREX.

Commercial Relationships: Sohaib R. Rufai, None; Hussein Almuhtaseb, Helena Lee, None; Richard Paul, None; Beth Stuart, None; Tony Kendrick, None; Andrew J. Lotery, Roche (R), Bayer (R)

Program Number: 3368 Poster Board Number: D0171
Presentation Time: 8:30 AM–10:15 AM
Ranibizumab treatment according to the subtypes of choroidal neovascularisation due to neovascular Age-related Macular Degeneration in a real-life. 3 years interim analysis of a French national observational and multicentric retrospective study: COLOR
David Sayag1, Florence Coscas2, Gerard Mimoun1, Catherine Favard1, Catherine François-Maury1, Valerie Krivosis2, Vincent Pierre-Kahn1, 1Rétina, Centre Exploration Vision, PARIS, France; 2Centre Ophthalmologique de l’Odéon, Paris, France; 3Centre Ophthalmologique d’Imagerie de l’École Militaire, Paris, France.

Purpose: To describe three years results of intravitreal (IVT) ranibizumab treatment in patients with neovascular age-related macular degeneration (nAMD) according to the subtypes of choroidal neovascularisation (CNV).

Methods: A retrospective, multicentric, non-interventional study conducted at 3 sites in France in October 2015. Patients aged ≥65 years with CNV secondary to nAMD treated with ranibizumab and followed up over 3 years between January 2007 and March 2015 were included. CNV lesions were classified as occult CNV (type 1), classic CNV (type 2) or retinal angiomatous proliferation (type 3). Treatment responses were monitored by visual acuity (VA) testing (ETDRS score), fluorescein angiography and optical coherence tomography (OCT). Data from patient’s medical charts were collected at diagnosis and at 3, 12, 24 and 36 months (±1 month) after ranibizumab initiation. Data from an interim analysis are presented here.

Results: A total of 143 patients (81 right eyes and 62 left eyes) were included in this interim analysis (92 females, 64.3%; mean age, 78.2±7.1 years). Mean time from initial diagnosis to start of ranibizumab was 3.4±13.1 weeks. Baseline VA was 58.6±14.6 ETDRS letters. Lesions were predominantly retrofoveal (n=106, 74.1%). CNV subtype was predominantly type 1 (70.6%), followed by type 2 (20.3%) and type 3 (9.1%). Mean number of IVT injections received in the first, second and third year was 5.5, 2.7 and 2.6 for type 1; 4.8, 2.7 and 2.0 for type 2, and 5.6, 3.1 and 2.5 for type 3, respectively. Three years’ treatment with ranibizumab resulted in visual acuity stabilization (mean BCVA: -0.4 letters). Fibrosis and atrophy progression were predominant in type 2 and type 3 lesions respectively. At Month 36, 106 (74.1%) patients were still receiving IVT ranibizumab and 8 were given other therapy; few had been switched to another anti-VEGF (n=3).

Conclusions: The results of this study show that VA was maintained after 3 years of IVT. Fibrosis and atrophy progressions seemed to be more related to type 2 and type 3 lesions, respectively.

Commercial Relationships: David Sayag, Florence Coscas, None; Gerard Mimoun, None; Catherine Favard, None; Catherine François-Maury, None; Valerie Krivosis, None; Vincent Pierre-Kahn, None

Support: NOVARTIS

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**Program Number:** 3369  
**Poster Board Number:** D0172  
**Presentation Time:** 8:30 AM–10:15 AM  
Anatomical and functional effects of subretinal rAAV.sVEGFR-1 gene therapy on retinal-choroidal structures in nonhuman primates  
Sharmila Vijay1, Kathryn W. Woodburn1, Pallavi Sharma1, Thomas W. Chalberg1, Vernard Woodley2, Jordan Attwood2, Matthew S. Lawrence2, Mehdi Gasmi1  
1 Avalanche Biotechnologies, Menlo Park, CA; 2 RxGen Inc, Hamden, CT.  
**Purpose:** Geographic atrophy has emerged as a potential complication in the chronic use of intravitreal VEGF inhibitors which are sometimes administered as frequently as every 4 weeks. This study was designed to determine whether this risk might exist in the setting of gene therapy vector-mediated expression of sVEGFR-1. The effect of sVEGFR-1 on the eye was evaluated for over a year following single dose subretinal administration of AVA-101 (rAAV. sVEGFR-1) adeno-associated virus (AAV) in nonhuman primates (NHPs).  
**Methods:** One group received subretinal injections of vehicle (100 µL formulation buffer) in both eyes (n=3; 1F/2M) with a second group receiving subretinal injections of 1x1011 vg rAAV. sVEGFR-1 in the right eye (n=8; 4F/4M) and no injection in the left eye. Eyes were evaluated every three months by slit lamp exam, fundus imaging, optical coherence tomography (OCT) and full-field electroretinography (ERG). Vitreous sVEGFR-1 levels were evaluated at 12 months to confirm AAV transgene transduction with further assessments, including histopathology, at 18 months. Results up to 12 months are presented here.  
**Results:** Subretinal administration of rAAV.sVEGFR-1 had no impact on the survival, clinical observations, clinical pathology, qualitative food consumption, retinal physiology as assessed by slit lamp exam, fundus imaging, optical coherence tomography (OCT) and full-field electroretinography (ERG). Observed departures from normal findings were limited to injection-induced changes associated with physical introduction of the injection cannula into the retina, resulting in RPE disruption in the immediate track of the cannula in a few cases, and stippled alteration of the light reflex from the RPE within the bleb area. Two eyes, K484 OS (receiving vehicle) and K478 OD (receiving vector) exhibited injection-associated inflammatory changes which resolved by month 6.  
**Conclusions:** Subretinal delivery of rAAV.sVEGFR-1 was well tolerated with no detectable geographic atrophy changes for over a year by a number of physiological and functional criteria. Histopathologic examination will occur at month 18 to further evaluate the chronic effects of continuous sVEGFR-1 expression.  
**Commercial Relationships:** Sharmila Vijay, Avalanche Biotechnologies; Kathryn W. Woodburn, Avalanche Biotechnologies; Pallavi Sharma, Avalanche Biotechnologies; Thomas W. Chalberg, Avalanche Biotechnologies (I), Avalanche Biotechnologies (C); Vernard Woodley, None; Jordan Attwood, None; Matthew S. Lawrence, None; Mehdi Gasmi, Avalanche Biotechnologies, Avalanche Biotechnologies (S).  

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**Program Number:** 3370  
**Poster Board Number:** D0173  
**Presentation Time:** 8:30 AM–10:15 AM  
6 weeks PRN intravitreal treatments results for macular diseases.  
**One year clinical practice data** Marcos J. Rubio Caso, Rahul Morwani Morwani, Carla Veiga Sanchez-Tinajero, Luis Arias Barquet, Josep Maria Caminal Mitjana.  
Hospital Universitari de Bellvitge, Sant Boi de llobregat - Barcelona, Spain.  
**Purpose:** PRN (Pro Re Nata) monthly treatment is the preferred treatment modality for most of the studies involving antiVEGF drugs. However, results obtained in actual clinical practice are lower that predicted due to the burden of monthly visits and injections. A 6 weeks PRN regimen can improve the accomplishment of patients while maintaining the benefits of treatment.  
**Methods:** Retrospective analysis of all patients treated with intravitreal injections from May 2014 to May 2015. Eyes with 6 or more visits and completed loading dose were selected for analysis. Disease activity were monitored with SD-OCT in all visits. Intravitreal injection were delivered in the same visit if needed. Group analysis were based on disease (AMD, DME and Vein occlusion) recording number of annual visits and injections. Visual acuity benefit was calculated for each group.  
**Results:** Data from 138 eyes from 127 patients were recorded. Total visits: 820. Total injections: 497. 100 eyes (72%) achieved 6 or more visits during the study period. Total visit average per year: 6.72. Total intravitreal injection averaged per year: 4.20. Total Visual acuity benefit: +0.57. AMD: Visits/year: 6.88. Injections/year: 4.05. VA changes from baseline: -0.33. DME: Visits/year: 6.77. Injections/ year: 4.76. VA changes from baseline: +0.71. Vein occlusion: Visits/ year: 6.71. Injections/year: 3.71. VA changes from baseline: +3.11. Drug use: Ranibizumab (64%), Aflibercept (27%), Ozurdex (5%), Avastin (4%). Switch of drugs: 18 eyes. Aflibercept: 13 cases, Ranibizumab: 2 cases. Ozurdex: 3 cases.  
**Conclusions:** 6 weeks PRN regimen can achieve a good balance between number of visits and drug efficiency use. Maintaining visual acuity is possible for a large number of patients while reducing the burden of intravitreal treatments.  
**Commercial Relationships:** Marcos J. Rubio Caso, Novartis (R), Bayer (R); Rahul Morwani Morwani, Carla Veiga Sanchez -Tinajero, None; Luis Arias Barquet, Novartis (R), Bayer (R); Josep Maria Caminal Mitjana, None