Intravenous Factor VII-Verteporfin for Targeted Photodynamic Therapy in Experimental Choroidal Neovascularization

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Purpose: To evaluate the efficacy and safety of factor VII-verteporfin for targeted photodynamic therapy (TPT) as compared to non-targeted photodynamic therapy (PDT) in a rat model of choroidal neovascularization (CNV). VII-verteporfin binds tightly and specifically to tissue factor, which is expressed on endothelial cells of CNV but not normal vasculature.

Methods: In Brown-Norway rats CNV lesions were induced by laser photocoagulation of the retina. After 3 weeks, the rats were injected intravenously with VII-verteporfin 0.5 mg/m^2 and 1.0 mg/m^2 or verteporfin 6.0 mg/m^2. Randomly selected lesions were treated with 689 nm laser 30 or 60 minutes later. Lesions were evaluated by fundus photography, fluorescein angiography and histopathology.

Results: The rats injected with verteporfin showed leakage in 75% of the CNV lesions on day 7 and 100% of lesions on day 14. The rats injected with VII-verteporfin at a dose of 0.5 mg/m^2 showed 33% and 36% of the CNV lesions on day 7 and day 14 respectively. When the dose was increased to 1.0 mg/m^2, leakage was detected in 25% and 23% of the CNV lesions on day 7 and day 14 respectively. No ocular side effect was detected by histopathologic evaluation.

Conclusions: The frequency of leakage in CNV lesions was significantly reduced using VII-verteporfin for targeted PDT as compared to non-targeted PDT. The efficacious dose with VII-verteporfin was about 1/10th of the dose usually used with verteporfin. Using VII-verteporfin for targeted PDT may improve the efficacy and safety of PDT for treating choroidal neovascularization.

C: R.A. Adelman, P.P. F. Lu, None; Z. Hu, P.P. J. Sinard, None; A. Garen, P.P.
Support: Leir Foundation, Research to Prevent Blindness

Comparison of Treatment Effects of Ranibizumab on Visual Acuity, Retinal Thickness and Retinal Morphology When Administered Monthly vs. Quarterly With Different Dosing Regimens in the Excite Trial

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Purpose: The effectiveness of regularly administered ranibizumab both on retinal function and retinal morphology has already been proven in many multi-center trials. The positive effects of the treatment initiation within the first 3 months of observation already have been reported. In this phase IIIb multi-center, randomized, active-controlled, double-masked “Excite” trial, after the loading phase of 3 monthly doses, the treatment effects were compared when ranibizumab was administered monthly versus quarterly with 0.3mg and 0.5 mg. Results: 333 patients at 54 study sites with diagnosis of subfoveal CNV due to AMD were included. Best-corrected visual acuity (BCVA) inclusion criterion was between 20/40 and 20/320. Patients were randomized 1:1:1 to receive 3 initial monthly injections of ranibizumab followed by quarterly injections of 0.3mg in group A, quarterly injections of 0.5mg in group B, and monthly injections of 0.3mg in group C. Change of BCVA letters score, mean central retinal thickness (CRT) in microns (µm) measured with optical coherence tomography (OCT) and appearance of cysts were monthly examined for all patients in all groups.

Results: All groups (120 versus 118 versus 115 patients in groups A,B and C) were balanced regarding age (75.0 to 75.8 years), gender (BCVA: 56.6% males and 43.4% females), CRT (314 ± 325 µm), lesion type and mean area of lesion (8.3 to 97.5 mm²) and CNV (8.13 to 94.6 mm²). At month 3 in all groups an equally statistically significant increase in BCVA (6.8, 6.6, 7.5 letters) occurred, as well as a statistically significant decrease in CRT (-101, -118, -96 µm) and decrease in appearance of intraretinal cysts. At months 6,9 and 12, one month after all groups were treated with ranibizumab, all groups presented similar CRT values, whereas at months 4.5, 7, 8, 10 and 11, one month after ranibizumab was only administered in group C, statistically significantly higher CRT values were observed in group A and B compared to group C. A higher increase in BCVA compared to baseline was shown at month 12 for group C (+8.3 letters compared to +4.9 and +3.8 in groups A and B, respectively). BCVA, CRT and appearance of cysts showed a high correlation for all visits (p<0.0001). The CRT values at month 12 were -96.0, -105.6, and -105.3 µm, in groups A, B, C respectively.

CR: C. Simader, None; M. Bolz, None; M. Ritter, None; I. Golbazi, None; C. Ahler, None; U. Schmidt-Erfurth, Novartis, C.
Support: None; CT: www.clinicaltrials.gov, NCT00725686
3095 - 2:45PM
Safety and Efficacy of Ranibizumab Treatment in Patients With Neovascular Age-Related Macular Degeneration: 12-Month Results of the SUSTAIN Study
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Purpose: To evaluate the safety and efficacy of individualized ranibizumab treatment over 12 months of patients with neovascular age-related macular degeneration (AMD).

Methods: In the prospective, multi-center, single-arm SUSTAIN study of 12 months duration, 513 ranibizumab-naïve AMD patients (results reported below) and 18 AMD patients from the ANCHOR study received 3 initial monthly injections of ranibizumab (0.3 mg) and re-treatment with ranibizumab (0.3/0.5 mg; one-third of patients switched to 0.3 mg during the study) in the maintenance phase when they either lost >5 letters in best-corrected visual acuity (BCVA) compared with the highest prior BCVA score or their central retinal thickness (CRT) increased by >100 μm from the lowest prior value measured by optical coherence tomography (OCT). No re-treatment was given when CRT was <225 μm or BCVA ≤79 letters. BCVA and CRT were assessed monthly using Early Treatment for Diabetic Retinopathy Study charts and optical coherence tomography, respectively.

Results: On average, patients were treated 2.7 times from Months 3 to 11. 21% of patients received no re-treatment in the maintenance phase. Serious adverse events (AEs) in the study eye: retinal hemorrhage (n=2), cataract (n=1), retinal pigment epithelial tear (n=1), reduced visual acuity (n=3), vitreous hemorrhage (n=1). Most frequent non-serious events: AEs: cardiac failure (n=6), myocordial infarction (n=5). Most frequent non-serious AEs: nasopharyngitis (n=10), hypertension (n=15). Most frequent ocular AEs: reduced visual acuity (n=95), retinal hemorrhage (n=37), increased intracranial pressure (n=36). Mean change in BCVA from baseline to Months 3 and 12 was 5.8 ± 5.3, and 3.6 ± 5.8 letters, respectively. Mean change in CRT from baseline to Months 3 and 12 was -30.1 ± 9.1 and 15.4 μm, respectively.

Conclusions: The incidence of AEs was comparable to previous pivotal clinical studies with ranibizumab. The efficacy results suggest that flexible dosing based on VA/CRT-guided re-treatment criteria may stabilize but does not increase BCVA above the levels achieved in the loading phase. Efficacy outcomes were achieved with a low average number of treatments.

Support: Novartis Pharma CT: www.clinicaltrials.gov, NCT00331864

3097 - 3:15PM
Safety and Intra-Ocular Anti-VEGF Injections: Observations in a Bevacizumab Cohort

Purpose: Ocular and systemic safety of intraocular Bevacizumab™ injections was studied in a cohort of 718 patients and compared to epidemiological data on cerebrovascular accidents (CVA), myocardial infarction (MCI) and mortality.

Methods: In a cohort of 718 patients (2648 injections), ocular and systemic safety was monitored from March-2006 till March-2008. The Dutch WHO and Epidemiological Rotterdam Study mortality, CVA and MCI data were used to create an age-matched group which provided expected incidences of CVA, MCI and mortality.

Results: Ocular adverse events included 1 endophthalmitis (0.038%), 7 uveitic episodes (0.264%), and 11 RIPS (0.415%). Systemic problems included 10 cases of CVA (1.416% per patient year (pPY)), 14 cases of MCI (1.981% pPY), 10 patients died during follow-up (1.416% pPY). No significant different incidences with epidemiological data were found for CVA (expected 74; observed 10, p=0.465) and MCI (expected 11; observed 10, p=0.55). In this cohort 10 patients died compared to the 38 expected mortalities p=3.8x10e-5. Analysis showed this group could determine safety for risk ratios of about 2.50x in MCI/CVA.

Conclusions: This study confirms earlier reports regarding the ocular and systemic safety of anti-VEGF intravitreal injections. As large placebo-controlled studies are not ethically possible, observed adverse event incidence should be compared with well-defined (age, gender, race) data of epidemiologic studies. In order to study small risk increases for MCI and CVA in the order of 1.25x-1.50x, data in groups larger than 10,000 patients using intra-ocular anti-VEGF therapy are required.

Support: None