Phase III study

The study VISION (VEGF Inhibition Study in Ocular Neovascularization) consists of two multicentric, randomized, prospective, controlled, dose-ranging and double-blinded phase III clinical trials, used for testing the safety and efficiency of pegaptanib sodium in the treatment of choroidal neovascularization secondary to AMD[(70)].

There were 1208 patients in this study, distributed by 117 centers and the main criteria for inclusion were: 50-year old or above with any kind of angiographic subtype of subfoveal choroidal neovascularization in the study eye secondary to AMD, with a lesion of 12 or below disc areas (including blood, scarring, atrophy and neovascularization).

The best-corrected visual acuity varied between 20/320 and 20/40.

Patients were randomized in four branches of the study: a group for simulation of pegaptanib intravitreous injections and one of three groups for administration of pegaptanib sodium intravitreous injections (with doses of 0,3 mg, 1mg or 3 mg).

The injections (or simulations) were performed with 6-week intervals for 48 weeks, in a maximum of 8 injections per patient.

All patients underwent the same procedures with exception of the scleral penetration performed in the group of intravitreous injection simulation.

The ophthalmologist performing the injections was not authorized to undertake the patients' follow up in order to guarantee the researcher's concealment.

For ethical reasons, treatment with PDT (Visudyne®) was allowed in some clinical centers in patients with mainly classic lesions, in all branches of the study and according to the researcher's criteria.

The primary study outcome measure was the proportion of patients who lost <15 letters of VA at the end of week 54.

Additional efficacy end-points included: proportion of patients maintaining or gaining > 0, 5, 10, or 15 letters, or losing > 30 letters (severe vision loss); mean changes in VA from baseline to week 54, and the proportion of patients with VA of 20/200 or worse in the study eye at week 54.

In total, 1186 subjects received at least one study treatment (mean, 8.5 of 9 possible injections)[(61)].

All pegaptanib doses were superior to sham with regard to loss of < 15 letters of VA: 70, 71 and 65% for 0.3 mg ($p < 0.001$), 1 mg ($p < 0.001$) and 3 mg ($p < 0.03$) groups,

respectively, versus 55% for sham.

Overall, the 0.3 mg dose was found to be most effective and further discussion is limited to the 0.3 mg (approved) dose.

Pegaptanib was significant superior to sham in the percentage of subjects maintaining or gaining 0, 5, 10 or 15 lines of vision ($p < 0.05$)[(71)].

Pegaptanib treated subjects were less likely to have severe vision loss (10 versus 22%, $p < 0.001$) or progress to VA < 20/200 (38 versus 56%; < 0.001).

Mean VA loss at week 54 was 7.95 letters for pegaptanib compared with 15.05 letters for sham
($p < 0.05$; 47% relative difference).

Treatment effect was independent of angiographic subtype, baseline VA and lesion size, sex, age, race or iris color[(71)]. VISION trial had an extension for 48 additional weeks.

Those patients receiving pegaptanib were randomized to either continue their pegaptanib dose or discontinue treatment.

Subjects initially receiving sham were rerandomized to continue or discontinue sham or to receive one of the three pegaptanib doses.

Overall, 1053 subjects were rerandomized; 941 (89%) were assessed at week 102 (mean, 15.7 of 17 possible total injections).

Compared with sham (sham over 2 years or randomized to discontinue sham in year 2), more of those receiving pegaptanib 0.3 mg during 2 years lost < 15 letters (45 versus 59%; $p < 0.05$).

Subjects continuing pegaptanib had the greatest benefits[(72)].

An exploratory analysis was conducted to assess the vision benefit of treating early subfoveal choroidal neovascularization secondary to AMD with pegaptanib in the VISION trials.

Subjects were grouped according to two different definitions of early disease.

Group 1 included those with lesions < 2 disc areas and a baseline VA of ≥ 54 letters, no prior PDT or laser photocoagulation and scarring or atrophy (n = 34 for pegaptanib 0.3 mg and n = 28 for sham).

Group 2 included those with occult with no classic CNV, with an absence of lipid and worse VA in the study eye versus the fellow eye (n = 30 for pegaptanib 0.3 mg and n = 35 for sham)[(70)].

At week 54, the responder rates (lost < 15 letters) were significantly higher for pegaptanib versus sham (group 1: 76 versus 50%; p = 0.03; group 2: 80 versus 57%; p = 0.05).

Pegaptanib-treated subjects in group 1 were approximately 10-times less likely to have severe vision loss than those receiving sham (3 versus 29%; p < 0.01); differences for group 2 were not as large (10 versus 17%; p = 0.17).

On average, subjects in both pegaptanib-treated groups lost less VA (group 1: -5.6 versus -16.6 letters; p < 0.01; group 2: -4.0 versus -16.7 letters; p < 0.006).

Notably, among those receiving pegaptanib 0.3 mg 12% of subjects in group 1 and 20% in group 2 gained ≥ 3 lines of vision, compared with 6% in the VISION study.

These findings suggest that pegaptanib treatment early in the course of wet AMD may improve visual outcomes[(65, 70)].

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