An empirical drug-disease model to characterize the effect of ranibizumab on disease progression in wet AMD patients

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1 – Introduction and objectives

Ranibizumab (Lucentis), an anti-vascular endothelial growth factor (VEGF) antibody Fab fragment is the standard of care for the wet form of age-related macular degeneration (wAMD) treatment reducing vessel leakiness and improving visual acuity by neutralizing VEGF in the retina.
There are still some medical needs for wAMD patients. Hence Lucentis database has been used to develop a disease model framework to support the development of new chemical entities.

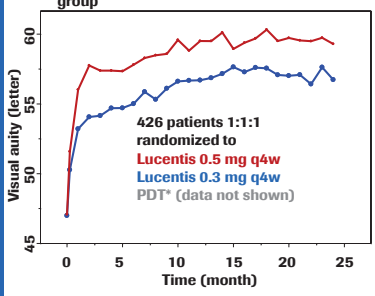
Objective: To characterize the time course of visual (VA) acuity of wAMD patients with or without anti-VEGF treatment. To understand the main drivers of wet AMD disease progression, response to treatment and also the impact of dose and dosing regimen

2 – Methods

The data

1) 24-month Patient level data on Visual acuity from three phase 3 and one phase 4 trials of ranibizumab (Lucentis) were available (n=2423 patients with several relevant baseline characteristics and including 300 untreated patients).
2) 2 of the phase 3 (Fig 1) data were used to develop the model while the other datasets were used for external evaluation (Fig 2)

Study 1: Mean VA time course by treatment group



Study 2: Mean VA time course by treatment group

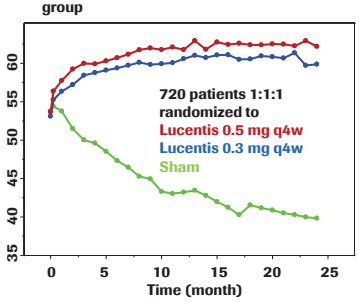
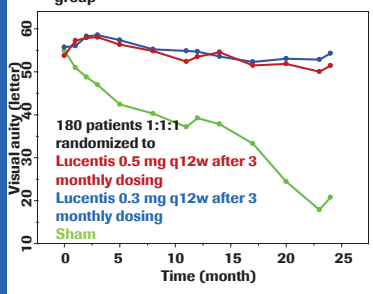


Fig 1: VA mean profiles of data used for the development of the model

Study 3: Mean VA time course by treatment group



Study 4: Mean VA time course by treatment group

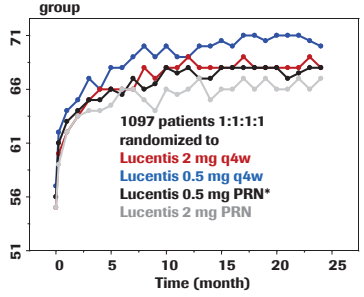


Fig 2: VA mean profiles of data used for the external evaluation of the model

Models

Two adaptations of the model in [1] were made : 1) use of a K-PD approach instead of dose to account for the change in dosing frequency over time. 2) use of an Emax model instead of an exponential to represent the drug effect (cf. equations 1 and 2).

Testing hypothesis: # 1. The drug does not affect the rate of progression of the disease (eq. 1)
2. The drug changes the rate of progression of the disease (eq. 2)

$$(1)\quad VA_t = VA_0 - (VA_0 - VA_{ss}) \cdot \left(1 - e^{-kpr \cdot t}\right) + \frac{E\max \cdot IR}{E50 + IR}$$

$$(2)\quad VA_t = VA_0 - (VA_0 - VA_{ss}) \cdot \left(1 - e^{-kpr\left(1 - \frac{IR}{Ed50 + IR}\right)t}\right) + \frac{E\max \cdot IR}{E50 + IR}$$

VAt, VA0 and Vass are respectively the visual acuity at time *t*, at entry in trial and at steady state when the patient is not under treatment. The quantity *IR* is proportional to the amount of drug a time *t*; *kpr* represents the rate of progression of the disease.
Hypothesis #2 suggests two sites of effect of Lucentis: a symptomatic effect (additive Emax) and a protective effect (effect on *kpr*).
Several baseline covariates were tested on model parameters.

Population data analysis

The data were modeled using a nonlinear mixed effects modeling approach in NONMEM (version 7.2 Icon Development Solutions, Ellicott City, MD) for the parameters estimation and SPLUS (version 8.0; Insightful, Seattle, WA) was used for graphical analyses of the results.
Residual variability was modeled with an additive error model.
Model development and qualification were guided by the objective function (OFV), the goodness of fit plots (GOF) and the precision of parameter estimates.

Key references:
[1] Satyendra et al. *Empirical Disease Progression Model for Ranibizumab in Age Related Macular Degeneration.* University of Tennessee Health Science Center, Memphis, TN, ACCP poster 2009
***PRN: Injections monthly for 3 months then as needed.**
*** PDT: photodynamic therapy**

3 – Results

Testing hypothesis

Under hypothesis #1 the rate of progression of the disease is not consistently predicted between dose groups (Fig 3) while under hypothesis 2, similar disease progression are predicted between dose groups (Fig 4). In addition the GOF and OFV were better under hypothesis 2.

Hypothesis 1 rejected in favor of hypothesis 2

The selected model (defined by eq. 2) suggests that the disease progression slowed down under Lucentis treatment (Fig 5).

Fig 3: Predicted VA deterioration (no treatment)

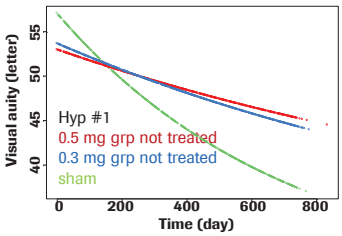


Fig 4: Predicted VA deterioration (no treatment)

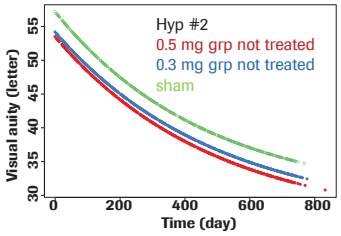
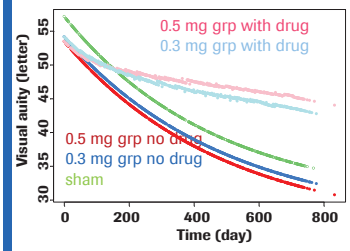


Fig 5: Disease progression w/o drug and w/ drug



Model suggests that Lucentis has 2 sites of effect: an additive (symptomatic) effect and a protective effect slowing down disease progression

Final model

The final model is as defined by (2) with baseline covariates on model parameters VA0, *Kpr* and E50. The covariates were found plausible and are all pathologic covariates. Goodness-of-fit plots (Fig 6) and a VPC (Fig 7) show that the model can describe adequately the data.

Fig 6: G-of-fit plots (all data of studies 1&2)

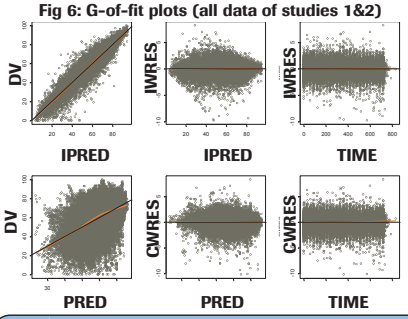
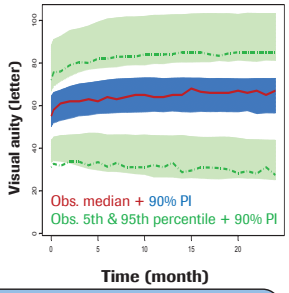


Fig 7: VPC study 2 (0.5 mg q4w)

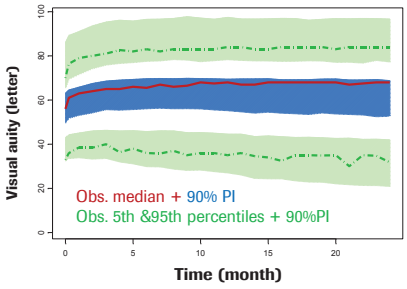


The potency of the symptomatic effect (*E50*) was 5 folds lower than the potency of the protective effect (*Ed50*) suggesting that ranibizumab is more potent for restoring the visual acuity than for slowing down wet AMD progression. The 0.3mg and 0.5 mg Lucentis are close to the Emax of the symptomatic effect but not so for the protective effect.

External evaluation

The final model was further tested successfully against studies 3&4 which are with different dosing regimen. As shown in Fig 8, typical trends of data not used during model development were well predicted while including only the baseline characteristics of corresponding patients. This highlights the importance of a K_PD approach which allows here to simulate different dosing regimens

Fig 8: VPC study 4 (0.5 mg PRN)



The external evaluation suggests that the model can suitably be used for clinical trial simulations

4 – Conclusions

The time dynamic of visual acuity for wet AMD patients with or without treatment was characterized using a disease model. The influences of several baseline pathologic covariates on model parameters were shown. The final model suggests two sites of effect of Ranibizumab: a symptomatic effect and an effect protective effect which slows down the progression of the disease. The low *E50* compared to *Ed50*, suggests that Ranibizumab is more potent for restoring the visual acuity than for protecting from the progression of the disease. Both doses (0.3 and 0.5 mg) with monthly regimen are close to the Emax of the symptomatic effect but not to the Emax of the protective effect. The K-PD approach has allowed to simulate successfully different dosing regimens suggesting that the model can suitably be used for clinical trial simulations. Our findings are in accordance with the work done in [1].