Indirect-Response Model For The Analysis Of Concentration-Effect Relationships In Clinical Trials Where Response Variables Are Scores

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Aim: Clinical effectiveness of many drugs can only be assessed in terms of scores quantifying the patient status (symptoms' intensity). Generally speaking scores are ordered categorical variables, however, when the number of categories is big enough they can be considered as continuous, though they are constrained and never exceed lower and upper limits. Also, drug effects on scores are indirect in nature that requires application of indirect response models (IRMs). A general IRM for clinical efficacy data was published previously [Piotrovsky V. Drug Efficacy Analysis as an Exercise in Dynamic (Indirect-Response) Population PK-PD Modeling. 11th PAGE Meeting, Paris, France, 2002].

This work was undertaken to demonstrate the application of such a model to efficacy data of two trials conducted in different centers. The results of the standard biostatistical analysis based on changes from a baseline observed at the last visit was controversial: the drug shows efficacy compared to placebo in one center, but not in the other one. Modeling exercise was aimed to identify possible reasons for this discrepancy in terms of IPM parameters.

Data: Efficacy endpoints and plasma drug levels were subject to concentration-response analysis. The score may take any integer value between 0 and 70. Study designs were similar: patients were randomized into parallel groups, and one group received placebo while others the active drug (Center 1: 8, 16 and 24 mg per day; Center 2: 16 and 24 mg). The overall duration of the studies was 22 weeks. The score was assessed at randomization and after approx. 4, 12 and 22 weeks of treatment. **Figure 1** shows the average scores per dose group *versus* week.

The population pharmacokinetic (PK) modeling was conducted and individual predictions of steady-state plasma concentrations (Css) to be used in further PK-efficacy modeling were obtained.

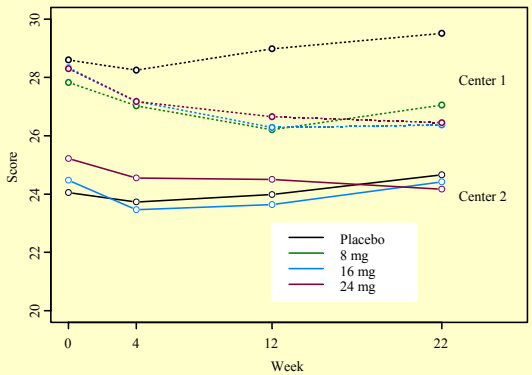

Figure 1: Mean score versus time profiles

Model: The rate of score change is a difference between the rates of deterioration (rD) and amelioration (rA):

$$dR/dt = rD - rA$$

Initial conditions are: R(0) = R0 ("baseline"). rA is assumed proportional to the current value of R, and the proportionality coefficient K (equilibration rate constant) indicates how fast the system stabilizes after a perturbation, e.g., treatment initiation:

$$dR/dt = rD - K*R \qquad (1)$$

It is assumed that the drug affects rD, namely reduces it. For convenience, rD is replaced by a parameter having the properties of scores. Since R is restricted dR/dt must tend towards zero when $t \to \infty$. The asymptotic value of R at $t \to \infty$, RP, will replace R in Eq 1: $rD - K*RP = 0$. rD can then be expressed via RP: $rD = K*RP$. Substituting this into Eq 1 gives:

$$dR/dt = K*(RP - R) \qquad (2)$$

Eq. 2 describes disease progression, and RP is an ultimate score: if RP>R0 the patient deteriorates otherwise he/she remains stable or spontaneously improves. K controls the rate of changes. The drug should thus reduce RP, and if the effect significantly exceeds that of placebo the drug is efficacious. RP becomes thus a composite parameter incorporating various (fixed and random) effects. To keep it within the boundaries these effects are considered in the logit domain:

$$RP = 70*\exp(\text{logit}(RP))/(1 + \exp(\text{logit}(RP))),$$

and their contribution is additive:

$$\text{logit}(RP) = \text{logit}(R0) + DP + EP + ED.$$

DP, EP and ED stand for disease progression, placebo and drug effects, respectively. According to this implementation, the disease progression is a shift in the logit domain. Graphical analysis of mean score *versus* time (**Figure 1**) show that after initial decrease due to drug/placebo effect R increases, and this may indicate the gradual weakening of one or both effects, in other words, long-term "tolerance". It is implemented as an exponential decay of EP and ED governed by a rate constant KT. "Tolerance" makes EP estimable: otherwise it cannot be separated from DP.

The steady-state plasma concentration of the drug, Css, was used as a predictor of the drug effect though an Emax model:

$$ED = E_{max}*Css/(C_{50} + Css)$$

Where E_{max} is a maximal drug effect in a logit domain, and C_{50} is a plasma concentration corresponding to the half-maximal effect. A linear concentration-effect model was also tested, but was found to be inferior. **Figure 2** shows the distribution of Css in various dose groups in Center 1 and 2. There are almost no differences in exposure between centers.

The fixed effect of the study center on R0 was included as it was evident from the data (**Figure 1**). Other effects were also tested using the likelihood ratio test (see **Results**). The model incorporated individual random effects on K, R0 and DP. The normal distribution and constant variance model was postulated for logit(R0) and DP. In the case of K the exponential variance model was assumed. All random effects were correlated except those on K and DP. The constant-variance residual error model was used.

Methods: NONMEM V software and the first-order conditional estimation method was used.

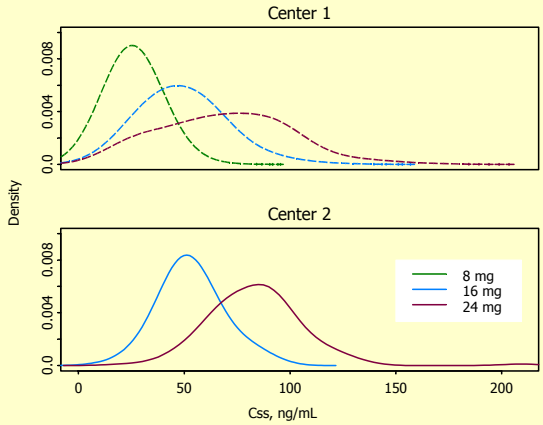

Figure 2. Steady-state drug concentrations in Center 1 and 2.

Results: The model provides a good fit as confirmed by the plot of observations *versus* population and individual predictions (**Figure 3**). **Figure 4** shows typical score profiles *versus* time.

In addition to study differences in the baseline score, K and C_{50} were found to differ significantly between centers (P<0.001). On the contrary, E_{max} and KT were the same:

	K (day^{-1})	C_{50} (ng/mL)	E_{max} (logit units)	KT (day^{-1})
Center 1:	0.00370	58.9	-0.975	0.00118
Center 2:	0.00268	235	idem	idem

This explains at least partly why the formal biostatistical analysis could not prove efficacy in the study conducted in Center 2. Firstly, most of patients of the 2nd study had Css much lower than C_{50} (see **Figure 5**). Secondly, the drug effect could not develop fully within the relatively short trial duration due to very low K, which determines how fast the system react on the changes in stimuli. The half-equilibration time was 27 and 37 weeks in Center 1 and 2, respectively. Other parameter estimates were DP=4.56 and EP=-4.85.

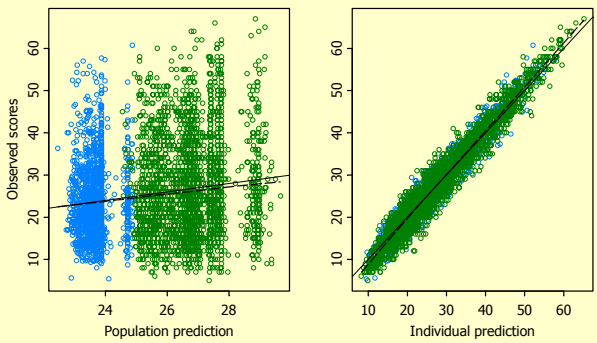

Figure 3. Goodness-of-fit plots

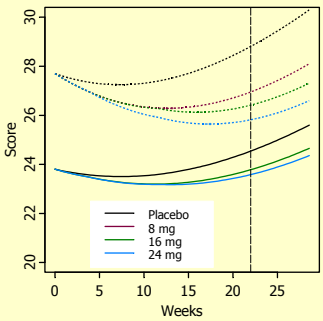

Figure 4. Predicted typical score *versus* time profiles

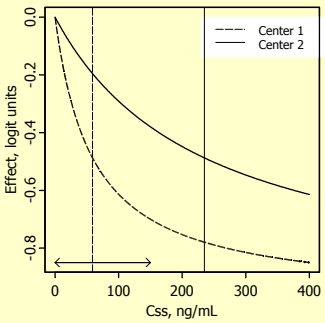

Figure 5. Predicted typical Css-effect profiles. The arrow at the bottom shows the Css range.

Conclusion: The model presents a platform for analysis and simulation of clinical efficacy/safety trials where endpoints are scores. It is still under development, in particular aimed to optimize random effects that is important for simulation to better design studies (determine an optimal trial duration, number of patients to be recruited, etc.). Another potential application can be prediction of clinical effects from in vitro (e.g. receptor binding) and preclinical studies.