

Do clinical pain scales correlate with target engagement? Inferences from a simulation-based analysis

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Introduction & Aim

Clinical scales are the preferred endpoint for the evaluation of efficacy during the development of analgesic and anti-inflammatory drugs. Doses in phase 2 and 3 trials are usually selected based on treatment response without taking the underlying pharmacological activity into consideration. The analysis of the efficacy relies on nominal doses, disregarding the characterisation of exposure-response relationships. Here we predict the effective Phase 3 dose range for GW406381, an investigational COX2 inhibitor in patients with rheumatoid arthritis based on the putative correlation between prostaglandin inhibition and the percentage improvement in symptoms (as defined by the ACRn index).

Subjects and Methods

Data from a phase 2b study in patients (n=540) with rheumatoid arthritis were available for the analysis. The ACRn, which was used as the primary efficacy endpoint, represents the percentage change in core symptom measures relative to baseline. First, a nonlinear mixed effects model describing placebo and drug effects was developed to characterise the time course of the pain response. A Weibull function including an *I_{max}* model was identified as the best descriptor of the observed response during treatment, which was defined as a change of at least 25% in scores relative to baseline. Trial subjects were then split into responders and non-responders; with model evaluation taking into account parameters and prediction errors for each group. In a second step, the clinical response (ACRn) was simulated in 4000 patients together with the putative biomarker concentrations using a model previously developed for prostaglandin (PGE2) inhibition. Finally, a non-parametric smoothing function (spline) was used to describe the non-linear correlation between ACRn and PGE2 inhibition.

The clinical scale was described by the expression below.

$$ACRn_t = OFF * \left(1 - P_{CSM} * \left(1 - \exp\left(-\frac{t}{td}\right)^\alpha \right) \right) * (1 - I_{COX})$$

where *ACRn_t* is the clinical endpoint at time *t*, *OFF* is the off-set baseline value, *P_{CSM}* is the estimate of the core set measure after placebo, *td*= time to reach the maximum placebo effect, *α*=shape parameter, *I_{COX}* represents the inhibitory drug effect derived from the relationship between drug concentrations and biomarker:

$$I_{COX} = \frac{I_{max} * Conc}{IC_{50} + Conc}$$

where *I_{max}* represents the maximum inhibitory effect, *IC₅₀* is the drug potency and *Conc* the systemic drug concentrations.

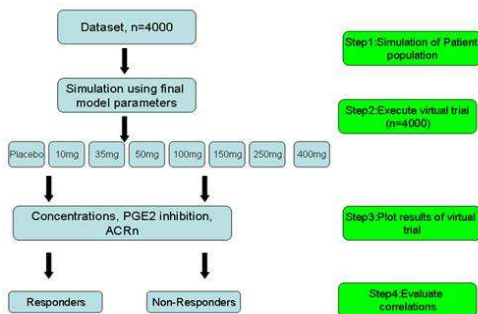


Figure 1. Overview of the simulation and correlation procedures.

Results

Modelling

The longitudinal response model described the data adequately. The percentage of responders was 54, 70, 59, 69 %, respectively for the placebo, 10, 35 and 50 mg dose groups, indicating little discrimination between dose and response. Although no significant covariate relationships have been identified, pharmacokinetic pharmacodynamic variability appears to cause most of the variation. The estimated *IC₅₀* had a wide distribution since there were potency differences amongst the responder phenotypes. Accordingly, prediction errors showed two different distributions in these sub-populations.

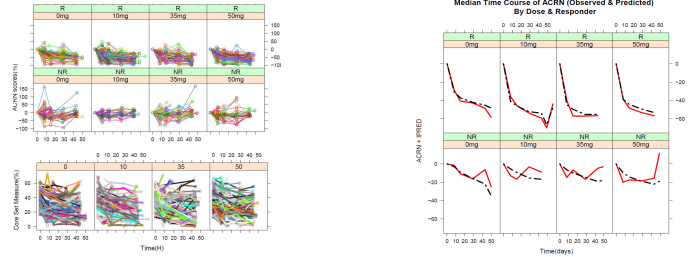


Figure 2. (Left) The time course of the observed ACRn (upper panel) stratified by dose level for responders and non-responders is summarised together with (lower panel) time course of the core set measures (CSM) for the overall population. (Right) Median time course of observed (solid) and model predicted (dashed) ACRn score in responders (R) and non-responders (NR) stratified by dose level.

Simulations

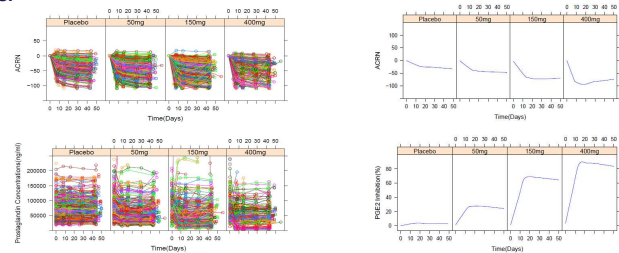


Figure 3. (Left) Predicted time course of simulated ACRn and the corresponding prostaglandin concentrations after administration of placebo, 50, 150 and 400mg GW406381. (Right) Predicted median time course of the simulated ACRn and corresponding PGE2 concentrations after administration of placebo, 50, 150 and 400mg GW406381.

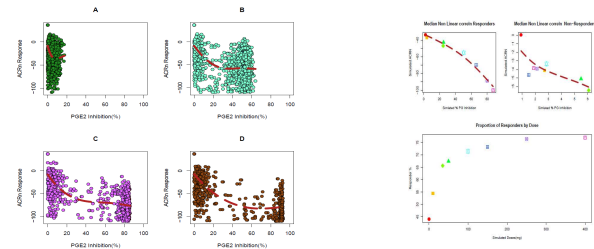


Figure 4. (Left) Non-linear correlation between PGE2 inhibition and the ACRn scores, stratified by dose level. The spline indicates the best fit. (Right) Fitting of the median PGE2 inhibition and ACRn for responders (upper panel A) and non-responders (upper panel, B). A clear correlation is observed between the relative proportion of responders and the dose of GW406381 (lower panel C). The symbols depict the different dose levels.

Based on the simulations, target inhibition (>80%) is expected at doses ≥250mg, whilst median ACRn reduction of >50% occurs at a dose ≥100mg. The proportion of responders increased nonlinearly across dose levels. Interestingly, the dose range used in the original clinical trial was far below that required for target engagement and consequently no significant differences were observed between placebo and active arms.

Discussion

Assessment of the exposure-response relationship for GW406381 yielded evidence of insufficient target engagement at low doses, explaining part of heterogeneity in drug response. Moreover, the decrease in ACRn over time could be mapped to PGE2 inhibition, i.e., a marker of target engagement and consequently a measure of the anti-inflammatory activity.

Given the nonlinear nature of the relationships between pharmacokinetics, biomarker and clinical improvement, the use of a biomarker-guided dose selection is essential to ensure that appropriate target engagement levels are reached in efficacy trials.