Comparison of NCA to Population PK in the Assessment of Bioequivalence for 2 Formulations of Trastuzumab

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INTRODUCTION

Non compartmental analysis (NCA) is considered the gold standard to demonstrate bioequivalence (BE), even though a NCA is highly dependant on times of sampling and known to be less appropriate in cases of nonlinear pharmacokinetics (PK). In many clinical circumstances, some or even all of the individuals may be sparsely sampled, making the individual evaluation and NCA difficult and less informative. In such cases, the use of models, in particular population models, becomes appealing. However, regulatory guidelines on the use of population pharmacokinetics (popPK) for demonstrating BE are currently lacking.

AIM

The objective of this study is to evaluate the use of PK parameters obtained by popPK for demonstrating BE compared to standard NCA.

METHODS

The data was obtained from a study specifically designed to demonstrate BE between two trastuzumab formulations (92 subjects received 5.95 mg/kg test- or 6.44 mg/kg reference [Herceptin®], and a single dose escalation (0.49, 1.48 or 2.96 mg/kg test product, 6 subjects each). Blood samples were collected up to 64 days after administration.

- A standard NCA was performed on original data of the BE study, using the software package R. Linear content-correction was applied, to correct for the dose difference between products. Area under the curve (from time 0 until end of experiment, calculated by trapezoidal rule) and maximum concentrations (Cmax) were obtained as measures for exposure.
- This approach was repeated with a reduced dataset, approximating alternative blood sampling times from literature[1].
- PopPK analyses included data from the dose escalation part and were performed on three subsets of the data; test product, reference product and combined data.
- Nonlinear mixed effects modelling (NONMEM 7.2) was applied for model development. In all popPK analyses, the effects of weight, height, age, body mass index, body surface area, lean body weight (LBW) and shed antigen were investigated on all PK parameters. Additionally, in the combined dataset, formulation was evaluated as covariate. The three popPK models were structurally similar to allow comparison between individual empirical Bayes estimates obtained by the three models. After model development, individual profiles were simulated, from which AUC (time 0 until 64 days) and C_{max} were calculated, identically to the NCA procedure.
- BE testing was performed by log transforming the data, calculating the test/reference ratio of the back-transformed geometric means of AUC (GMR_{AUC}) and C_{max} (GMR_{Cmax}) and their 90%-confidence interval (CI) using SAS 9.1.3. BE testing was done on exposure results of the BE dataset (NCA-RD), the reduced dataset (NCA-AD), the combined data model (COMB) and the combined data of the single product models (TESTREF)

RESULTS

- 3-compartmental models with combined linear and Michaelis Menten clearance best described the data (Fig. 1) .
  - For the models of the BE and dose escalation data separately, interindividual variability was identified for central V, the V_{max} and the k_e
  - For the combined data, interindividual variability was identified for central V, the K_M and the k_e
- Residual variability was best described by a combined error model
- Normalised lean body weight was identified as covariate on central V.
- 'Formulation' was no significant covariate, indicating BE.

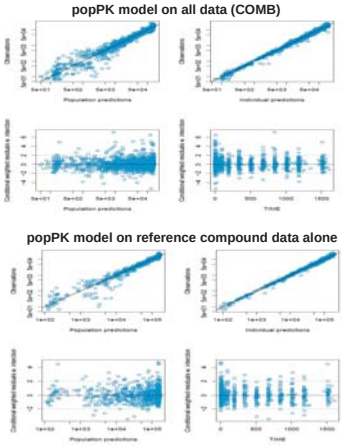

Fig. 1 Diagnostic plots for the three population PK models. For each models the four plots indicate data (circles) and line of unity (black line).

RESULTS cont.

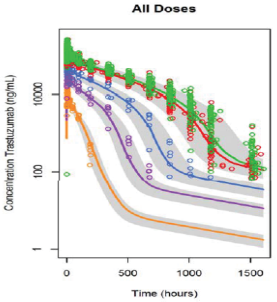

Fig. 2 Visual predictive check of the combined data model. The lines represent s the median predicted concentration-time profile for each dose with their 95% prediction interval (grey), for each dose with their observations (circles). Doses: yellow to red; ascending doses of test product and green represents reference product

- 95% of the data lie within the 95% prediction interval of the combined model (Fig 2), indicating good predictive properties of the model.
- Due to the non-linear behaviour, dose correction for the doses 0.49, 1.48 and 2.96 mg/kg cannot be performed using standard NCA methods

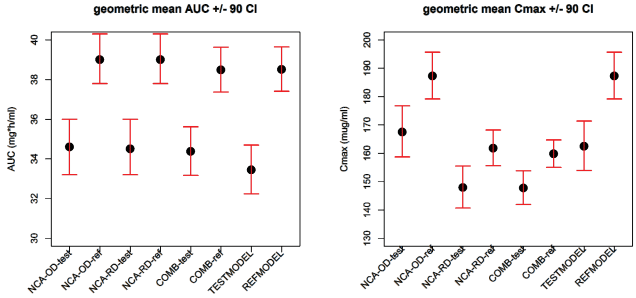

Figure 3: separate NCA results for test and reference on original data (OD), reduced dataset (RD) and model simulations (COMB, TESTMODEL and REFMODEL)

- The 90% CI of the AUCs are overlapping per product for all approaches (Fig 3)
- The 90% CI of the Cmax are not overlapping between the NCA-OD and NCA-RD, showing the dependence on time of sampling for standard NCA methods
- The 90% CI for Cmax is significantly reduced in the COMB model

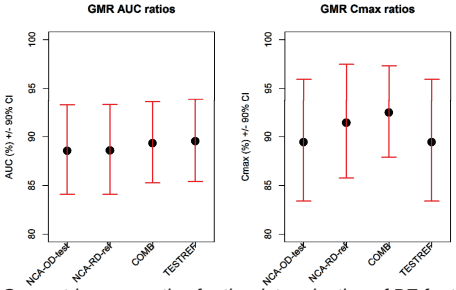

Figure 4: Geometric mean ratios for the determination of BE for the original data (OD) and model simulations (COMB and TESTREF)

- All GMRs for AUC and Cmax significantly deviate from 1 (P<0.05)
- All GMR 90% CIs overlap for both AUC and Cmax
- The 90% CIs are well within BE limits (i.e. 80-125%).

CONCLUSIONS

- The BE results from the population models are indistinguishable from the standard NCA, confirming the applicability of popPK for the evaluation of BE.

DISCUSSION

In contrast to the raw data points used for the NCA, the models describe the full concentration-time profiles thereby capturing the nonlinearity, interindividual variability, residual variability and covariates in PK parameters.

- PK models have improved predictive properties for other dosing regimens in further drug development when compared to standard NCA.

Additional data should be obtained after administration of reference product doses of 0.49, 1.48 and 2.96 mg/kg to confirm the predictive properties of the model and confirm the usefulness of popPK for BE with regard to dose correction

References

[1] Yin et al, BJCP 2014 78(6); 1281-90

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