Impact of covariate model building methods on the evaluation of clinical relevance of covariate effects in population pharmacokinetic analysis

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OBJECTIVE

To evaluate and compare the adequacy of decisions on covariates clinical relevance using full model and SCM.

METHODS

Covariate modeling approaches

Full model

Addition of the covariate to the base model

SCM

Scrubbing the covariates

Simulation study

Data simulation

- Inspired from a real case study conducted on N = 387 hemophilia A patients, a X-linked recessive deficiency of factor VIII (FVIII) activity resulting in lifelong bleeding, treated with emicizumab, a monoclonal antibody developed for on-demand prophylaxis of bleeding. From 5 clinical studies, 5 = 200 datasets simulated with two models (derived from the model developped by Retout et al. [3])
  - Base model: one compartment model with first order absorption and linear elimination + body weight (BW) effect on V/F and CL/F
  - Covariate model: base model + age and black (BLK) race effect on V/F and age and albumin (ALB) effect on CL/F

- Number of patients, PK sampling schema (mixing patients with either rich or sparse schema) and covariate distributions similar to the real data

Estimation

- PK data analysis performed with NONMEM version 7.4
- First order conditional estimation with interaction (FOCEi) algorithm for parameters estimation
- SE were derived from the covariance matrix computed as R**1/2** with R = the Hessian and the Cross-Product Gradient matrix, respectively

Covariate investigation

- Full model and SCM applied to each of the simulated datasets
  - SCM = BW effect not included in the set of covariates to investigate (structural covariate)
  - SCM with BW selection = BW effect included in the set of covariates to investigate

Covariate effect ratios calculation

Continuous covariates

- Ratio between the covariate effect value computed at the 10th and 90th quantile of the observed covariate distribution (Q10 or Q90) and the covariate effect value computed at the median (MED)

Categorical covariates

- Ratio between the covariate effect value of one category and the covariate effect value of the reference category

RESULTS

Evaluation

- Plot upsets of the different model combinations obtained with SCM and FREM
- Relative estimation errors (REE) of ratio estimates

REE of ratio estimates

- Low REE of the ratio estimates (around 5%, not exceeding 40%)
- Overall, unbiased ratio estimates
- Wider variability of the ratio estimates with the full model, as all the covariate effects are estimated; unlike SCM due to the selection process
- Same variability of the ratio estimates with the full model and SCM when the covariate is selected

Covariate clinical relevance decisions

- Overall, similar conclusions on covariate effect clinical relevance were obtained with the reference model, the full model and SCM
- BW effect on CL/F and V/F is always clinically relevant (R) with the full model and SCM
- Age effect on CL/F and V/F, ALB effect on CL/F and BLK effect on V/F are found significant (S) in more than 90% and 85% of the cases with the full model and SCM, respectively
- Covariate effects simulated at 0 are found non-relevant (NR) or with insufficient information (I) to conclude with the full model in more than 95% of the cases and non-significant (NS) in more than 80% of the cases

CONCLUSION

Covariate effect ratios were unbiased with both full model and SCM. SCM seems to perform better in terms of estimation precision thanks to the selection process when no effects are simulated. The evaluation of clinical relevance of covariate effects was satisfactory for the two approaches. Because of the selection process, significant covariates may sometimes not be selected with SCM. Some additional methods such as SCM plus and FREM will also be investigated. These methods deserve to be evaluated in a context of more complex simulated covariate model or sparse data.

References