Girish Aras and Wenjing Yang - Separation in Logistic Regression

The logistic regression model is widely used to describe the active treatment effect on a binary response variable. Complete/Quasi-complete separation is a common problem people encounter when computing logistic regression equation, especially in the presence of a zero count in any one of the cells in a 2x2 table. In that case, existing fitting techniques fail to converge to the correct answer. Targeting the separation problem, we explored various remedy methods, including exact solutions and Firth’s bias-reduced maximum likelihood estimate approach (Firth, 1993), etc. Practical suggestions are given based on the comparison among remedy methods. Firth, D. (1993). Bias reduction of maximum likelihood estimates. Biometrika, 80, 27-38.

Huei Wang and Yan Zheng - Chain Procedures and Gatekeeping Strategy for Hierarchical-Structured Hypotheses with Clinical Trial Applications

Chain procedures (Millen, B and Dmitrienko, A; 2010) are utilized the initial allocation of the overall alpha level among the null hypotheses of interest and the process for interactively reallocating available or unspent alpha among the remaining eligible null hypotheses. Chain procedures are more flexible than popular stepwise gatekeeping strategy such as Holm or fallback procedure. Gatekeeping strategy for hierarchical-structured hypotheses proposed by Yan Zheng (2011 submitted) satisfies relaxed both conditions: (1) the overall significance of the primary family, the probability of at least one hypothesis in the primary family to be significant, will not be affected by the significance of the secondary family (2) significance of the secondary hypotheses can not be claimed if none of the primary hypotheses is significant. This poster will introduce both methods and apply the clinical data to these 2 methods.

Xuena Wang, Matthew Guo, Helen Wei, Kun Nie, and Xuesong Guan - Evaluation of Alternative Dosing Rule in Use of romiplostim by Simulations

Alternative dosing rules may be raised up with interest from different aspects of safety review. Given very limited available trial data which is usually based on one promising dosing rule, we evaluated alternative dosing rules by simulations. Models were built under assumptions to capture the algorithm following dosing rules with parameters initialized using available trial data. With simulated data, we were able to compare alternative dosing rules and confirmed that the current FDA dosing rule had better performance. Methods were demonstrated using Amgen romiplostim studies.
Purpose: For a novel fixed-dose triple combination of olmesartan (OM), amlodipine (AML), and hydrochlorothiazide (HCTZ), modeling and simulation was undertaken to predict the blood pressure-lowering effect for triple therapy dose combinations not included in the pivotal Phase III study. Methods: The analysis utilized data from the pivotal Phase III study along with thirteen Phase I and two prior Phase III studies spanning development programs for OM, OM+AML, OM+HCTZ, and the triple combination. Modeling characterized the compounds’ population pharmacokinetics and subsequently linked individual exposures to the observed blood pressure-lowering effects for seated trough diastolic (SeDBP) and systolic (SeSBP) blood pressure. The blood pressure-lowering effects for all combinations were then simulated for the Phase III population based on the collective set of models.

Results: Two-compartment models with first-order absorption adequately characterized the population pharmacokinetics of each compound. Consistent with previous findings, creatinine clearance was a significant predictor for OM clearance; age was a significant predictor for AML clearance; and sex, age, and creatinine clearance were each significant predictors for HCTZ clearance. Observed SeDBP and SeSBP were described well by the model-predicted steady-state areas-under-the-curve of OM, AML and HCTZ. Blood pressure lowering effects were modeled as a sum of placebo and drug effect, where drug effect consisted of the individual compounds’ effects and interaction among them. The drug effects of OM and AML were saturable, while that of HCTZ was proportional to its exposure. Triple combination therapies had superior blood pressure-lowering effects compared to their respective monotherapies and dual combination therapies. The order of the blood pressure lowering effects among the different dose-strengths of the OM/AML/HCTZ mg combination was 20/5/12.5<40/5/12.5<(40/10/12.5=40/5/25)<40/10/25 (mg).

Conclusion: Modeling and simulation quantified the blood-pressure lowering effect of dose combinations not included in the pivotal Phase III study. Results of the modeling and simulation were included in the filing package for the triple-combination therapy.

Encore from the American Society of Hypertension Annual Meeting New York City May 1, 2010.
Bing Gao, Jing Huang, Jae Kim, Brian Smith, Lisa Hendricks, Scott Wasserman - Meta-analysis on Phase 1 Monoclonal Antibody Studies with Placebo Subcutaneous Injections to Evaluate the Relationship between Injection Site Reaction Adverse Events and Injection Volume

Background: A monoclonal antibody (mAb) investigational product is entering phase 2 trials with high injection volume. To better understand the relationship between tolerability and injection volume, we performed a meta-analysis pooling information from placebo subjects with subcutaneous (SC) administration of existing early phase mAb programs.

Methods and Results: All available and completed phase 1 mAb studies with SC administration of placebo were included in the analysis (13 studies; total N=128). Sixteen injection site reaction AEs (AEoI) were observed and listed with study, treatment, and baseline details. Incidence rates are summarized by study in a forest plot with point estimates and 95% CIs. One study with substantially more AEoIs and a different incidence rate was detected as a potential high-impact study. Analyses were performed with and without this study on (1) AEoI incidence rate tabulation within low, medium and high injection volume subgroups; (2) logistic regression of injection volume on incidence of AEoI (Y vs. N) dynamically adjusting for baseline covariates by forward selection procedures.

Conclusions: There is not sufficient evidence to suggest that higher injection volumes could lead to higher incidence rate of AEoIs: the incidence rate tabulation does not show any clear trend, and injection volumes are not a significant factor in the logistic regression model with and without the high impact study.

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Erik Rasmussen, Jian-Feng Lu, Yu-Nien Sun, and Mike Hale - Case Study in Oncology of Exposure-Response Modeling Guiding Choice of Dosing Regimen for Confirmatory Studies

One case study will be discussed where exposure-response modeling of phase 2 data guided the dosing regimen for confirmatory studies in ovarian cancer. No MTD was identified in the FIH study and further dose finding was designed in a phase 2 study in recurrent ovarian cancer. Due to practical constraints this study had only three arms: 1) placebo controlled, 2) low dose, 3) high dose. Exposure-response analyses of the data indicated that the highest exposures were associated with the best efficacy and an appropriate safety profile. Based on these analyses, the dose in confirmatory studies was chosen to be 50% higher than the maximum phase 2 dose. Potential issues that would lead to misleading conclusions from this exposure-response analysis will be discussed.

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Exposure-response relationship is important for the determination of dose or range of doses of drug candidates based on the safety and effectiveness. Exposure characterizes drug concentration-time course in body fluids resulting from administration of a dosage of a drug. (i.e. PK). Response refers to a measure of the pharmacologic effect of the drug (i.e. PD). Exposure response analysis is used to describe a pharmacodynamic response (such as efficacy or safety response) as a function of drug concentrations and pharmacokinetic behaviors (exposure). The analysis can be utilized to identify a target concentration range expected to provide therapeutic benefit and thus aid the selection of appropriate dosing regimen for drug development. In this presentation, method of the exposure response will be discussed with an example for a phase 2 oncology trial. Challenges of the analyses such as effect of confounding prognostic factors, assessment of causality of the association, survivorship bias, imputation bias and limitation of the design will also be discussed with proposed solutions.