CERTARA

Application Note: Clinical Trial Modeling and Simulation

Modeling the effects of genetic variation using Pharsight Trial Simulator V2.1

Introduction

Computer simulation provides an effective means for evaluating whether a clinical trial design is efficient and optimally informative with a high likelihood of success. Many variables affect the likelihood of success of a trial, and genetic variation in the population is being evaluated with increasing frequency for its impact on trial outcomes. The Pharsight Trial Simulator V2.1 software provides a platform to simultaneously model the effects of pharmacokinetic and pharmacodynamic (PK/PD) variables, including genetic variation, in order to explore the sensitivity of a clinical trial design to various sources of uncertainty.

Trial Simulator utilizes Monte Carlo simulations to approximate the distribution of probable outcomes for a clinical trial. The simulations are based on a stochastic model describing drug disposition and effects over time in individual subjects. Outcomes are modeled as a function of subject characteristics, including drug and disease effects, any genetic covariates, and random factors. Each simulation draws a new set of subjects from a virtual population based on a user-defined model of covariates and their distributions in different subpopulations. The model, covariates, and trial protocol specifications provide the framework for simulating the range of possible outcomes for a trial. Models can be modified to compare a variety of scenarios, to test their sensitivity to various uncertainties, as well as to explore alternative designs that might improve the robustness, informativeness, or certainty of success for a clinical trial.

This Application Note illustrates the capabilities of Trial Simulator to model genetic covariates along with other sources of variability. To protect proprietary information, the example presented is based on historical literature data, not current drug development practices. Certara is available to assist you in developing models based on the latest data and your specific requirements.

Background

Human immunodeficiency virus (HIV) causes chronic depletion of CD4+ cells, which leads to cancers and opportunistic infections characteristic of AIDS. Zidovudine (ZDV) inhibits HIV replication *in vitro* and slows progression to acquired immunodeficiency syndrome (AIDS) in HIV-positive subjects.

Version 15 Features

- PBPK model for antibody drug conjugates
- Enhancement of transporter capabilities
- Development of the Simcyp Monkey
- Esterase metabolism
- Pharmaceutical capabilities
- Introduction of the M-ADAM (multiple-layer gut wall within ADAM) model
- Introduction of the pediatric biologics model
- Animal PBPK-PD developments
- Parameter estimation and ASA expansions
- Development of the lung model
- Simcyp command line console

Protocol 019 of the AIDS Clinical Trial Group (ACTG 019) was a multi-center, randomized, double-blind, Phase III trial in asymptomatic HIV-infected subjects. The findings showed a decreased risk of AIDS progression or death with ZDV treatment, especially in subjects with baseline CD4+ cell counts greater than 300/cc.[1]

The chemokine receptor 5 (CCR5) is a cell surface receptor used by the HIV-1 virus to enter CD4+ cells.[2] Data suggests that resistance to HIV-1 entry into CD4+ cells may be caused by mutations in the CCR5 gene.[3-5] A 32-base pair deletion in the CCR5 gene (D32) causes a frameshift and premature termination of translation, and has been associated with resistance to HIV infection and slower rate of progression to AIDS. The D32 deletion occurs with different frequencies in different racial groups. Of particular relevance, one study reported that individuals with one copy of the D32 deletion showed more favorable reductions in HIV RNA levels from baseline after 24 weeks of ZDV treatment than individuals with two normal CCR5 genes.[6]

Building the model

Trial Simulator provides a graphical user interface to enter the available information to construct a model of a drug's action. Data from ACTG 019 was used to construct a model with a 24-month treatment phase, and placebo, 500 mg/day ZDV, and 1500 mg/day ZDV treatment arms. The primary endpoint was time until inefficacy, which was tested using survival analysis at the 5% Type I error rate.

Simulated observations included plasma concentration and dropouts, where dropouts (due to inefficacy) were sampled every 28 days. Enrollment was set at 1500 subjects, with 500 subjects in each treatment arm.

Covariates related to AIDS demographics

Covariate distributions for AIDS demographics were based on published information, including the 1997 *HIV/AIDS Surveillance Report*.[7] A hypothetical "default" population included 70% male and 30% female subjects from a suburban testing center. Weight was modeled as a normal bivariate distribution with gender status where males averaged 73 kg and females averaged 60 kg. The CD4+ cell count covariate was modeled with a mean of 348/cc (SD=90) and a range of 0-500/cc. Methadone use was modeled in 4.4% of subjects.[7]

The race of the simulated suburban population was Caucasian, where the genotype frequencies are:

Status	Abbreviation	Frequency
Two normal CCR5 genes	+_+	0.81
One normal, one D32 gene	+_D32	0.18
Two genes with D32	D32_D32	0.01

Definition of subpopulations

Trial Simulator allows subpopulations to be created that have different characteristics from the default population. The effect of enrolling strictly from the default population can then be compared to enrolling a fraction of the subjects from a subpopulation. We can test the trial design's sensitivity to varying genotype frequencies caused by differences in the racial composition of prospective recruitment sites, by creating a subpopulation with a different genotype frequency. In this example, a sub-population was created that represents prospective subjects near a city center site, where 60% of the subjects were Asian and 40% Caucasian.

The genotype frequencies for this mixed population were:

Status	Abbreviation	Frequency
Two normal CCR5 genes	+_+	0.924
One normal, one D32 gene	+_D32	0.072
Two genes with D32	D32_D32	0.004

In addition, methadone usage at the city center was modeled to be roughly twice as high, or 8.0%.[7]

In this example, individuals with the genotype D32_D32 were excluded from enrolling using the exclusion criteria feature, since the model assumed that individuals with this genotype are not observed in HIV-1 infected populations, as suggested by literature in this domain. This assumption could be modified and the effect on trial outcome assessed in additional simulation scenarios.

The pharmacokinetic model

The model for drug action was created in Trial Simulator using the reported PK of ZDV. The ZDV clearance was modeled as CL = 1.3 $\pm$ 0.3 (L/h/kg), with clearance related to body weight as CL (L/day) = CL (L/kg/h) x weight (kg) x (24hr/day).[8] Clearance was assumed to decrease by 40% in methadone users,[9] and decrease by 20% in women, independent of weight.[10]

Pharmacodynamic model

The overall hazard of disease progression was modeled as a function of the survival hazard for placebo and factors accounting for the improved survival in subjects taking the antiretroviral treatment, having CD4+ cell counts of 300/cc or greater, and CCR5 genotype. The influence of the antiretroviral drug was modeled as an E_{max} function of the drug concentration and the IC50 (concentration producing half-maximal viral inhibition). The hazard function for time to inefficacy was expressed as:

$$h_{inefficacy} = h_p \times \exp(\beta CD4 \times XCD4+ \beta ARVD \times C/(C + IC50))$$

Where C equaled 0, 0.23, and 0.68 mg/L for placebo, 500 mg, and 1500 mg/day ZDV doses, the IC50 value equaled 0.013 mg/L,[11] ßARVD (AntiRetroViralDrug) equaled –0.49 (E_{max}), XCD4 is the CD4+ cell count, and ßCD4 is a parameter. An E_{max} value similar to that of ZDV was assumed in these simulations. In the ACTG 019 study, 81% of the placebo subjects did not experience inefficacy for two years. Hence, the daily hazard rate utilized in these simulations was h_p = 0.000288/day. Hazard due to toxicity was modeled in a similar fashion.

Time to inefficacy of ZDV treatment over 2 years was modeled to be variable depending on CD4+ cell count status. For this model, CD4+ cell count status was modeled as a function of genetic effects at the CCR5 gene, with the genetic effects having a downstream indirect effect on ZDV efficacy reflected in the survival probabilities.

The model for genetic effects on CD4+ cells is based on evidence indicating that among HIV-1 positive individuals, there was a shift towards slower loss of CD4+ T cells in subjects with at least one copy of the CCR5 D32 allele (mean slope of –42 cells/year) as compared to subjects with no copies of the CCR5 D32 allele (mean slope of –105 cells/year), a 40% difference.[3] In these simulations, a smaller difference (20%) and a larger difference (60%) were compared, to examine the sensitivity of the trial design to the uncertainty in the magnitude of this effect. The size of this genetic effect could be further modified to explore other scenarios.

The effects of more than one gene could be modeled. For example, another gene might be known to have an effect on ZDV response that is equal, independent, and dominant (one copy of a mutant allele confers the same advantage as having two copies of the mutant allele).

Using Trial Simulator, any of these parameters could be modified to explore other plausible scenarios with respect to equality of genetic effects, independence, and type of gene action.

Definition of scenarios to be compared

The goal of these simulations is to assess the impact of population variation, and the magnitude of the effect, of the CCR5 genotype on the power of the trial. Four scenarios were simulated. Thirty replicates were simulated for each of the four scenarios. In two scenarios, 1500 virtual subjects were enrolled from the suburban site. In the other two scenarios, 1500 virtual subjects were enrolled from the city center. To explore the effect of the CCR5 D32 allele, this effect was modeled to be smaller than the data suggests (20%) in two of the scenarios, and larger than the data suggests (60%) in the other two scenarios.

These four scenarios compared the power of the design to demonstrate ZDV efficacy across a range of uncertainty in the effect of CCR5 genotype, as well as varying genotype frequencies within the population that might result from recruiting at sites with different racial demographics.

Simulation results

The clinical trial simulated in this example measured survival time to inefficacy, which was defined as the combined endpoint of death, opportunistic infection, or AIDS-related complex in asymptomatic HIV-infected subjects.

The goal of each simulated clinical trial was to show that ZDV affected the survival of patients versus placebo using a survival test with a Type I error rate of 5%. For each replicate simulated, the data were analyzed using a log-rank analysis of survival, and the P-value from that analysis was saved. Each trial simulation was classified as a "success" or "failure" depending on whether the P-value was less than or greater than 0.05, respectively. The results were then summarized using the graphics and analytical tools featured in the Trial Simulator software.

The distribution of P-values is shown using box plots in the figure above. The shaded squares represent the middle 50% of the P-values, with 25% being both above and below the square. Outlying individual P-values are shown by the single horizontal lines. Power is calculated as the proportion of P-values less than 0.05. These results show that the suburban site had greater power than the city center, regardless of the value of the genetic effect. Because of its reduced power, the city center might be preferable only in the context of some other compensating factor, such as a substantially faster projected recruitment rate than at the suburban site. Using the data summarization tool in Trial Simulator, the percent of the simulations that produced a P-value of 0.05 or less was calculated for each scenario, as shown below.

Scenario	Power + Err
City GE20	53% + 9%
City GE60	70% + 8%
Suburb GE20	80% + 7%
Suburb GE60	67% + 9%

From these results, we see that the impact of the size of the genetic effect of the D32 allele is also fairly substantial. Only in the scenario 3 (suburban site, 20% difference in CD4 cell loss due to CCR5 genotype) does the power reach 80%, and provide a high enough likelihood of success to actually execute the study design scenario.

A variety of strategies to improve the power of the design could be explored using Trial Simulator, including increasing the sample size, changing the inclusion or exclusion criteria with respect to the CCR5 genotypes, or modifying the design to reduce the impact of the D32 allele.

We hypothesize that a larger effect of the D32 allele (60% vs 20%) increases power in the city center by prolonging survival. However, in the suburban site, where survival is already prolonged due to reduced methadone use, additional prolongation due to a larger D32 effect makes differentiating between ZDV and placebo more difficult. This results in the reduction in power observed at the suburban site with increasing D32 effect size.

In this example, there is an interaction between the allele frequency in population and magnitude of the effect of the variant allele. This type of interaction may be more common than many researchers realize. Due to the impracticalities of actually executing more than one trial design scenario, these interactions can only be explored through modeling and simulation approaches.

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BR Jun 2016 v2 082916