Safety monitoring of a kidney transplant study using a Bayesian time-to-event model

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Introduction

Studies to investigate new treatments to prevent acute kidney allograft rejection are typically active controlled studies with a primary endpoint of Month 6 biopsy-proven acute rejection (BPAR). When designing these studies, there is a strong desire to monitor the study in an on-going fashion and use formal stopping rules to stop the study quickly if the rejection risk with the experimental treatment is unacceptably high. However, because the endpoint can be 6 months from randomization, stopping rules based on the observed data meeting the primary endpoint at Month 6 can be inefficient. We desired a model and stopping rule that allowed for formal incorporation of historical control data and that does not require waiting until subjects reach the Month 6 endpoint. To this end we examined stopping criteria based on estimates from a Bayesian time to event model for BPAR.

Our approach is presented in the context of a Phase 2 study investigating CP-690,550, an immunosuppressive agent being developed for the prevention of kidney allograft rejection and other autoimmune diseases.

In a previous Phase 2a study in *de novo* renal allograft recipients, CP-690,550 15 mg BID, in combination with MMF, achieved a 6-month BPAR rate similar to Tacrolimus plus MMF.

In the planned study, the dosing regimen was altered and the patient population was broadened.

Current Study Design
A Phase 2, randomized, multicenter, partially blinded, active-comparator controlled parallel-group trial. Approximately 300 patients were to be randomized to one of two CP-690,550 regimens or cyclosporine (CsA).

Study objective: To compare the incidence of clinical BPAR of combination regimens of CP-690,550 and mycophenolate mofetil (MMF) / mycophenolate sodium (MPS) versus a cyclosporine (CsA)-based regimen in recipients of first renal allografts at Month 6 post-transplant.

Methods

Without accrual pauses to follow patients until each has reached their endpoint at 6 months, analyses must utilize partial information from many patients.

To accomplish this we incorporated a time-to-event model for BPAR. Since no subjects will have reached the Month 6 endpoint early in recruitment, a Bayesian model facilitated predictions of Month 6 BPAR early in the study.

Likelihood
• A piecewise-exponential (PE) survival model with hazard rate parameters λ_1, λ_2, and λ_3 for the control arm.
• A constant hazard ratio (ρ) to describe the effect of CP-690,550.

For the PE model, the likelihood contribution for each individual is

$$\rho^{x_i y_i} \lambda_j^{y_i} e^{-H(t_i)}$$

where x_i is an indicator (=1) for subjects in the CP-690,550 group, y_i is an indicator (=1) for subjects with BPAR, and H(t) is the cumulative hazard.

The resulting likelihood function is

$$L(\theta) = \prod_{j=1}^{3} \lambda_j^{N_j^C} e^{-\lambda_j S_j^C} \left(\rho\lambda_j\right)^{N_j^E} e^{-\rho\lambda_j S_j^E}$$

where N_i^C and N_i^E are the number of subjects in the control group and the CP-690,550 groups with a BPAR in the jth interval and S_i^C and S_i^E are the corresponding person-times at risk for BPAR in the jth interval.

Prior distributions

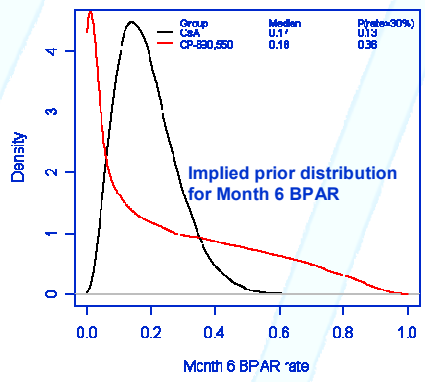
$$\pi(\theta) = \pi(\rho)\prod_j \pi(\lambda_j)$$

$$\lambda_j \sim Gamma(\alpha_j, \beta_j) \quad j = 1,2,3; \quad E(\lambda_j) = \alpha_j / (\alpha_j + \beta_j)$$

$$\log\rho \sim N(\mu, \sigma^2)$$

α_j and β_j can be viewed as the prior number of events in interval j and the prior patient-time in interval j.

Values for α_j and β_j were derived by meta-analysis of K-M estimates of time to BPAR ([1]-[4]). Weakly informative prior for log(ρ), centered at treatment effect (μ=0, σ=1).



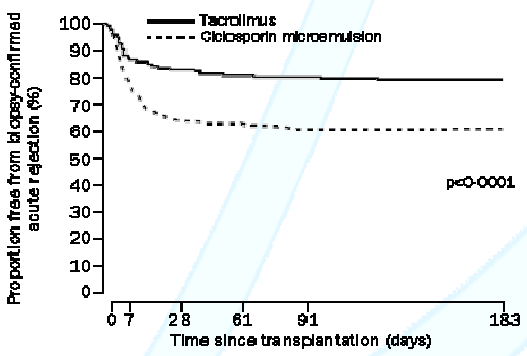
Posterior distribution

$$\pi(\theta \mid data) \propto \prod_{j=1}^{3} \lambda_j^{N_j^C + N_j^E + \alpha_j - 1} e^{-\lambda_j\left(S_j^C + \rho S_j^E + \beta_j\right)} (\rho)^{N_j^E} e^{-(\log\rho - \mu)^2 / 2\sigma^2}$$

Samples from the posterior distribution were obtained by sampling from
• $\pi(\rho \mid data)$ using direct sampling over a fine, discrete grid

• $\pi(\lambda_j \mid \rho, data) \sim Gamma\left(N_j^C + N_j^E + \alpha_j, S_j^C + \rho S_j^E + \beta_j\right)$

Bayesian time-to-event model
A review of the published literature identified 4 studies with designs and dosing regimens matching the study control regimen ([1] – [4]). Review of the Kaplan-Meier time-to-event curves from these and other studies suggested dividing the 6 month treatment interval into 3 time periods with approximately constant hazard rates: Days 0-7, Days 8-28 and Days 29-182. An example K-M curve is shown below ([5]).



Stopping Guidelines
Unacceptable risk was defined as a high probability that the BPAR risk for the CP-690,550 group is larger than that of the control group and an absolute risk of BPAR in the CP-690,550 group that > 30%. Thus we evaluated stopping guidelines of the form

Stop if $P\left(BPAR_{M6}^E > BPAR_{M6}^C \mid Data\right) > p_{diff}$

and $P\left(BPAR_{M6}^E > 30\% \mid Data\right) > p_{abs}$

where $BPAR^E_{M6}$ and $BPAR^C_{M6}$ are the Month 6 BPAR rate in the CP-690,550 and CsA groups, respectively.

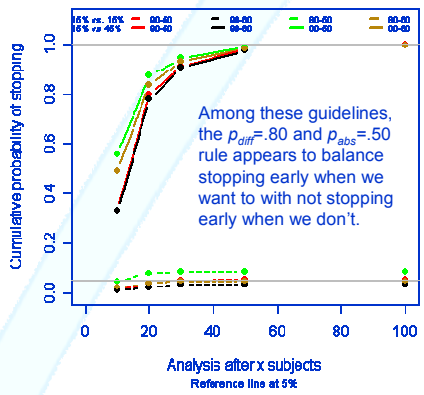
Using simulation, we evaluated different stopping guidelines by looking at different combinations of p_{diff} and p_{abs}. We compared these to frequentist rules based on the log-rank test and Fisher's exact test.

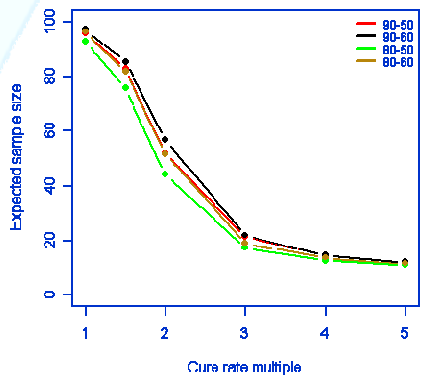
A wide variety of scenarios were simulated, including:
• An exponential cure-rate model such that $BPAR^C_{M6}$ = 10%, 15%, and 20% and $BPAR^E_{M6}$=1x, 2x, 3x, 4x and 5x $BPAR^C_{M6}$

Results

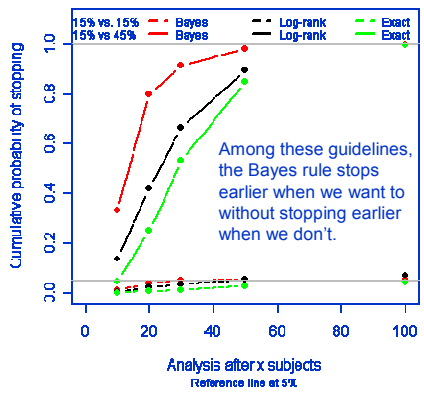
Plots of simulation results from the exponential cure rate model with 15% BPAR are shown below.

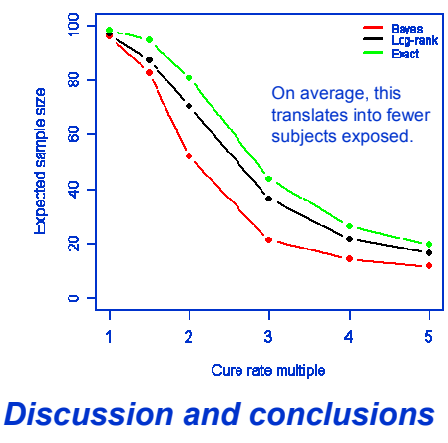
Comparison of 4 Bayesian stopping guidelines





Comparison of Bayesian and simple Frequentist stopping guidelines





Discussion and conclusions

• The Bayesian stopping rules considered here appear to be superior to ones based on log-rank test and Fisher's exact test.

• The use of weakly informative priors provided a balance of the desire to use what we "know" with the desire to make decisions based on the current study.

• This approach is most useful for monitoring a trial early in its conduct, when there are very limited trial data, but decisions to continue or terminate the trial must be made to protect patients in the trial

• This approach is similar in spirit to work of Rosner [6] and Thall et al. [7].

• Work is on-going to generalize this model to an exposure-response model.

• Extensions may include modifying the prior distributions for the hazard rates to allow a smooth transition between intervals [8]

References

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