Using short-term evidence to predict 6-month outcomes in clinical trials of signs and symptoms in rheumatoid arthritis

Nixon RM¹, Bansback N², Stevens JW¹, Brennan A³, and Madan J³

¹Modeling & Simulation, Novartis Pharma AG, Basel, Switzerland; ²Centre for Health Evaluation and Outcome Sciences, St. Paul’s Hospital, Vancouver, Canada; and ³Health Economics and Decision Science, Sheffield School of Health and Related Research, University of Sheffield, the UK.

Background

What is rheumatoid arthritis?
- A chronic, systemic inflammatory disorder that principally attacks the joints producing an inflammatory synovitis that often progresses to destruction of the articular cartilage.

What is an ACR20 and ACR50 response?
- Composite binary measures of response of a patient to RA treatment. Essentially, ACR (American college of rheumatology) 20 and ACR50 correspond to a 20% and a 50% improvement over a period of time.

What do we want to know?
- We have a new biologic treatment for RA. We want to predict the ACR response after 6 months of treatment.

What data do we have?
- Data from a 1-month clinical trial. This gives the number of patients who have an ACR response after treatment with the new biologic drug for 1 month.
- Summary data from the literature on other biologic drugs. This gives the number of patients who have an ACR response at 1 and 6 months.

Objective

To develop a model to predict the probability of an ACR20 and ACR50 response after 6 months for a new biologic drug for rheumatoid arthritis, when 1-month ACR20 and ACR50 response data are available.

Model

- "j" denotes the treatment arm within each trial and 'k' denotes the treatment type used (1=MTX; 2=biologic monotherapy; 3=biologic plus MTX).

Model checking – Bayesian predictive P-values

What are Bayesian predictive P-values?
- One sided tail probabilities that the data predicted by the model are more extreme compared to the observed data.

- This is a goodness-of-fit approach to assess the validity of a model.

- For the new drug, ACR20 at 1 month. ACR20 = 30 and ACR50 = 15.

- Find the probability of a response at 6 months via a uniform distribution.

- Plot the observed ACR response at 1 and 6 months.

- Plot estimated ACR response at 1 month and 6 months.

- Find the probability of a response at 6 months

- For the literature data from existing biologics

- Plot the observed or estimated ACR20 and ACR50 response

- New drug

- Plot estimated ACR at 1 and 6 months

- The horizontal green line shows the uncertainty in the estimated response at 1 month.

- The vertical green line shows the uncertainty in the predicted response at 6 months (Figure 3).

- Uncertainty in the predicted response includes uncertainty in ACR measured in the trial and uncertainty in the prediction model.

Main model assumptions

- The probability of response at 6 months depends upon the probability of response at 1 month through a logistic regression.

- The logistic regression has a slope parameter, that is independent of the study arms, and an intercept parameter that is dependent upon the particular study arm.

- Intercept parameter is normally distributed random effect, with a different random effect mean for each type of treatment.

- This acknowledges the existence of heterogeneity between trial arms. We are assuming that each treatment arm is exchangeable with any other, even across the clinical trials themselves.

- Number of patients in arm

- Mean intercept for each treatment

- Trial specific random effect intercept

Using the model for prediction

- Suppose a clinical trial for the new drug has 30 patients and 15 of them have an ACR20 response at 1 month. ACR20 = 30 and ACR50 = 15.

- Find the probability of a response at 6 months via a uniform distribution.

- For the new drug

- Plot the observed ACR response at 1 and 6 months.

- The horizontal green line shows the uncertainty in the estimated response at 1 month.

- The vertical green line shows the uncertainty in the predicted response at 6 months (Figure 3).

- Uncertainty in the predicted response includes uncertainty in ACR measured in the trial and uncertainty in the prediction model.

Figure 1: Distribution for a predicted data point. Shaded area shows the predictive P-value

Figure 2: Plot of the quantiles of the predictive P-values against the theoretical quantiles assuming the model is correct.

Figure 3: Plot of the observed or estimated ACR20 responses at 1 and 6 months.

References


This study was supported by Novartis Pharma AG, Basel, Switzerland. Copyright © 2009 Novartis Pharma AG, Basel, Switzerland. All rights reserved.