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The use of an ordered multinomial logit model in network analysis: an example in psoriatic arthritis

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Introduction

Network meta-analyses provide us with a framework for considering all relevant data in estimating relative treatment effects across treatments, using both direct (head-to-head comparisons) and indirect evidence. In using such analyses, it is important that careful consideration is given to the type of outcome data being utilised in the analysis to ensure that an appropriate model choice is made.

We recently undertook a project for the UK National Institute for Health and Clinical Excellence (NICE) to evaluate the effectiveness and cost-effectiveness of three anti-TNF agents, infliximab, adalimumab and etanercept, for the treatment of psoriatic arthritis (PsA).[1] There are several outcomes which are routinely used to measure disease activity in PsA, and whilst a number of these were considered in the project only one outcome is discussed in this poster: the Psoriasis Area and Severity Index (PASI). The American College of Rheumatology score (ACR) was evaluated using the same model and is reported in full elsewhere.[1]

Methods

We undertook an independent systematic review and a critical appraisal of three company submissions on behalf of NICE.[1] These sources identified six RCTs, two for each of the treatments being evaluated (infliximab, etanercept and adalimumab). Each trial compared the active therapy with placebo. No trials compared the active therapies head-to-head. Outcomes were evaluated at randomisation and after three months of therapy. There were some data gaps, as one of the trials did not report PASI 90 scores and one trial reported no PASI scores.[1]

The PASI scores are reported in the clinical trials as discrete outcomes, although they represent a continuous outcome ranging from 0 to 100%. Each of the trials reported the outcomes at three different percentage levels PASI 50, 75 and 90, such that if a patient achieved PASI 50, this meant his or her PASI score had improved by 50% or more since randomisation and so on. In pooling the data we used a multinomial ordered logit model to maintain the relationship between the three outcome levels (see Box 1). Because more than one RCT evaluated each treatment, the model is hierarchical to respect the randomised nature of the comparisons. The models were implemented in WinBUGS version 14 with non-informative priors.

The probability of an outcome was calculated by estimating a latent variable as a linear function of the independent variable (randomised treatment) plus a set of thresholds/cut-off points. The "latent variable" represents the (unobserved) continuous improvement in PASI score that was used to construct the reported PASI 50, 75 and 90 outcomes. To facilitate modelling some assumptions were required:

- Common effects were assumed for each treatment class (etanercept, infliximab, adalimiumab) (N.B., a random effects model was also tested as a sensitivity analysis);
- Thresholds were assumed to be fixed across trials;
- The baseline latent variable (i.e., the response to placebo) was allowed to be independent for each trial.

Box 1: Interpretation of the coefficients of the hierarchical ordered logit model

The intercept (alpha i) represents the mean improvement in the placebo arm of trial i, measured in terms of the (unobserved) continuous PASI score. The coefficients represent the mean improvement that can be attributed to each treatment, again measured in terms of the unobserved continuous PASI score. As this is an ordered logit model, the coefficients beta_1, beta_2 and beta_3 can be interpreted as the log-treatment effect of each drug relative to placebo.

Inputs

Data inputs n/N (%)		
Mease 2000	Etanercept	Placebo
PASI 50	8/19 (42)	4/19 (42)
PASI 75	5/19 (26)	0/19 (26)
Mease 2004	Etanercept	Placebo
PASI 50	31/66 (47)	11/62 (18)
PASI 75	15/66 (23)	2/62 (3)
PASI 90	4/66 (6)	2/62 (3)
IMPACT	Infliximab	Placebo
PASI 50	22/22 (100)	0/16 (0)
PASI 75	15/22 (68.2)	0/16 (0)
PASI 90	8/22 (36.4%)	0/16 (0)
IMPACT 2*	Infliximab	Placebo
ADEPT	Adalimumab	Placebo
PASI 50	50/69 (72)	10/69 (14)
PASI 75	34/69 (49)	3/69 (4)
PASI 90	21/69 (30)	0/69 (0)

IMPACT 2 data was commercial in confidence so is not presented in the results table.

Results

Probability of PASI response				
Outcome	Intervention	mean	Credible intervals	
			2.50%	97.50%
PASI 50	Placebo	0.13	0.092	0.175
	Etanercept	0.403	0.236	0.592
	Infliximab	0.913	0.823	0.968
	Adalimumab	0.738	0.552	0.881
PASI 75	Placebo	0.044	0.028	0.065
	Etanercept	0.177	0.085	0.313
	Infliximab	0.769	0.594	0.901
	Adalimumab	0.477	0.275	0.693
PASI 90	Placebo	0.018	0.01	0.026
	Etanercept	0.074	0.032	0.145
	Infliximab	0.557	0.347	0.767
	Adalimumab	0.257	0.12	0.452

Concluding remarks

This study used a hierarchical ordered logit model to synthesise multinomial data from several trials. The model was implemented using Bayesian software, WinBUGS. This model could also have been fitted from a frequentist perspective, for example, using the GLLAMM package in STATA; however, there are advantages in using WinBUGS. It is a very flexible piece of software which can accommodate alternative specifications of a model and is able to present results in a variety of different ways, with ranging levels of detail depending on the needs of the user. In this instance the network meta-analysis using a hierarchical ordered logit model has allowed us the flexibility to fully capture the relationship between the scores, whilst maintaining the randomisation of the original trials. Had we elected to model one of the scores as a discrete outcome, relevant information would have been lost and the likelihood of spurious results would have increased. Whether a Bayesian or frequentist approach is adopted, it is crucial that the statistical model brings together all of the relevant evidence, and respects the randomised structure of the data and the relationships between the outcomes.

References

1. Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, Myers L, Bruce I, Chalmers R, Sutton A, Sculpher M, Woolacott N. Etanercept, Infliximab and Adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(10):1-329