Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in Rheumatoid Arthritis

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Summary

Mixed treatment comparison (MTC) is a generalisation of meta-analysis. Instead of the same treatment for a disease being tested in a number of studies, a number of different interventions are considered. Meta-regression is also a generalisation of meta-analysis where an attempt is made to explain the heterogeneity between the treatment effects in the studies by regressing on study-level covariables. Our focus is where there are several different treatments considered in a number of randomized controlled trials in a specific disease, the same treatment can be applied in several arms within a study, and where differences in efficacy can be explained by differences in the study settings. We develop methods for simultaneously comparing several treatments and adjusting for study level covariables by combining ideas from MTC and meta-regression.

We use a case study from rheumatoid arthritis. We identified relevant trials of biologic verses standard therapy or placebo and extracted the doses, comparators and patient baseline characteristics. Efficacy is measured using the log odds ratio of achieving six-month ACR50 responder status. A random-effects meta-regression model is fitted which adjusts the log odds ratio for study level prognostic factors. A different random effect distribution on the log odds ratios is allowed for each different treatment. The odds ratio is found as a function of the prognostic factors for each treatment. The apparent differences in the randomised trials between TNF-$\propto$ antagonists are explained by differences in prognostic factors and the analysis suggest that these drugs as a class are not different from each other.

1. Introduction

We use a case study from rheumatoid arthritis (RA). The discovery that the inhibition of Tumor Necrosis Factor alpha (TNF-$\propto$) and Interleukin 1 (IL-1) may reduce the manifestations of RA, improving function and retarding radiological progression has led to the development of novel treatments (1). We refer to these treatments as biologics. Previously the early initiation of disease modifying anti-rheumatic drugs (DMARDs) like the antimetabolite methotrexate (MTX), were considered the most successful strategy for delaying the progression in this chronic inflammatory disease (2). We study the currently licensed treatments, the TNF-$\propto$ antagonists adalimumab (Humira), infliximab (Remicade) and etanercept (Enbrel) along with the IL-1 inhibitor anakinra (Kineret). A number of systematic reviews of these biologic therapies have confirmed their safety and efficacy in placebo controlled trials (3-8). Efficacy in RA trials is determined using the American College of Rheumatology (ACR)

improvement criteria, a measure which combines a core set of disease activity measures. An ACR50 requires a 50% reduction in the tender joint count, a 50% reduction in the swollen joint count, and a 50% reduction in 3 of 5 additional measures including patient global assessment, physician global assessment, pain, disability and an acute-phase reactant (9). However, most trials have been performed on relatively small and diverse patient populations.

Meta-analysis attempts to combine the results from a number of studies that address a set of related research hypotheses. These studies may have been performed amongst different patient groups and with methodological differences, so heterogeneity between trials is expected with the true effects in each study not being identical. In a random-effects meta-analysis a random-effects distribution is placed on these effects sizes, and the mean used as the estimate of the overall mean.

Mixed treatment comparison evidence synthesis is an extension of meta-analysis (10). Instead of all studies comparing the same treatment with the same comparator, different comparisons are made. Mixed treatment comparisons enable estimates of intervention effects to be estimated that are not directly observed, or observed intervention effect estimates to be strengthened from indirect estimates. For example, no head-to-head study of etanercept and infliximab exists, but this could be estimated from studies comparing etanercept versus placebo and studies comparing infliximab versus placebo. We are concerned with a connected network of randomized controlled trials (11), where several studies consider a collection of new interventions. Two deviations from a standard mixed treatment comparison are found in this study. Firstly, MTX is sometimes used in both the placebo arm and in combination with a biologic in the treatment arm, sometimes it is only used in the control arm, and sometimes it is not used at all. Secondly multiple treatment arms of the same drug are used in each of the studies, each using different doses and / or timing regimes.

Meta-regression attempts to explain the difference between intervention effects in a collection of studies (12). Figure 1 shows how the average disease duration of the patients in the studies relates to the log odds ratio of an ACR50 event. A weighted linear regression is fitted to this relationship. While this has many shortfalls; it ignores the heterogeneity between the studies and all the mixed treatment comparison features described above, it does demonstrate the clear relationship between disease duration and the relative effectiveness of biologic treatments versus control. Meta-regression attempts to explain the difference in log odds ACR50 response between studies by regressing this effect sizes from each study onto the disease duration for each study. The effect sizes, adjusted for study level characteristics, will

not be identical, as the regression will not completely explain the heterogeneity, so a random-effects distribution is placed on the adjusted effects sizes.

A previous meta-analysis compared the three therapies that target TNF-∝ (6). However this focussed on trials which were of a more similar design. Since then, the number of studies has doubled, and includes many in patient populations with early disease where the efficacy of the comparator arm is relatively high.

The objective of this paper is to combine standard meta-regression techniques and ideas from mixed treatment comparisons to perform indirect comparisons. The case study aims to find the odds ratio of an ACR50 event at six months if treated with a biologic in comparison to control. We examine how the odds ratio for the relative effectiveness of biologic therapy versus control varies with different important study level covariates and compare the odds ratios for the four licensed biologic treatments.

2. Methods

2.1. Literature search and data extraction

A comprehensive and systematic literature search was performed. Reports of randomised controlled trials of biologic agents compared with placebo or methotrexate published between 1 January 1980 to 1 January 2005 were identified. Five electronic bibliographies were searched, covering biomedical, science, social science and grey literature [Cochrane Library, MEDLINE, EMBASE, DARE, Scientific Citation Index] The MeSH search used in Medline, Embase, and the NHS Database of Reviews of Effectiveness (DARE) consisted of three steps, each containing any possible MeSH relevant to the target condition [rheumatoid arthritis], study drug [biologic or TNF-a or IL-1 or etanercept, adalimumab, infliximab or anakinra], and study method [randomized controlled trial]. We searched the Scientific Citation Index and Cochrane Library with the keywords rheumatoid arthritis along with proceedings from the main rheumatology meetings and Food and Drug Administration (FDA) submissions.

The initial screen of the search results identified 107 reports which were potentially relevant. When we applied the filter that studies had to be randomised controlled trials comparing biologic agents to a placebo in patients with RA, only 60 reports remained. We applied a secondary filter to remove trials with a horizon less than 6 months (the point when the full potential of biologic therapy is generally reached), trials which did not report the primary measure of synthesis (the ACR response

criteria) and trials that did not use a conventional comparison to methotrexate or placebo.

Thirteen RCTs (27 individual reports) were included in the final analysis. Data are given in Table 1. Four of these studied adalimumab (13-16), three studied anakinra (17-19), four studied etanercept (20-23), and two studied infliximab (24;25). The average baseline disease duration varied from between one and 14 years and mean baseline Health Assessment Questionnaire Disability Index (HAQ-DI, the primary measure of disability in patients with RA) ranged from 1.3 to 1.9.

2.2. Model development

When a binary outcome is being explored in a meta-regression is it best to use the raw outcome counts as this avoids using an estimated standard error of the log odds ratio (12). There are many possible study and patient level covariates that could be used to explain the heterogeneity. With relatively few studies, multiple analyses using all study level covariables will have a high probability of finding a spurious explanatory variable. Further there are insufficient degrees of freedom to sensibly model many covariables. We chose two covariables, disease duration (mean years), (26) and baseline HAQ-DI (a measure of disability) (27), which were measured in all identified trials and are known to have prognostic value in determining the effect of treatment.

The studies used in the meta-regression are all randomised controlled trials. However, the meta-regression finds a relationship between the log odds ratio of the ACR50 outcome and study level characteristics, but these study level characteristics have not been randomised, so the regression can be regarded as an observational relationship. Two of the studies (ASPIRE 2004(24) and PREMIER 2005(13)) have missing data for the six month ACR measure. These studies are in patients with newly diagnosed RA, which may be systematically different from trials in patients with established disease. This lack of 6 month ACR50 data could lead to biased estimated treatment effects for infliximab and adalimumab. Even though meta-regression, adjusting for disease duration, may go some way to redress this bias, it is unrealistic to suppose that it would fully adjust the analysis. To deal with this we have assumed that the missing six-month ACR50 outcomes can be estimated by the 12-months ACR50 outcomes available in these two studies.

For the statistical modelling, our notation is as follows: i =1…13 denotes the study index; j=0…J_i the arm within the study, where 0 indexes the control group and J_i is the number of treatment regimes being tested in study i; k_i denotes the biologic agent used in study i, where 1 indicates anakinra, 2 etanercept, 3 infliximab and 4

adalimumab. n_{ij} denotes the number of patients in arm *j* of study *i*; r_{ij} the number of patients achieving ACR50. m_{ij} is an indicator variable for treatment with MTX, they are 1 if a biologic agent or MTX is given in arm *j* of study *i* and 0 otherwise. Two study-level covariates are also included: x_{1i} is the average disease duration, and x_{2i} the average baseline HAQ for each study. These two covariates are re-centred about their means across studies to aid model fitting.

2.2.1. Model 1 – Mixed treatment comparison model with univariate random effects

Assume each patient in arm *j* of study *i* independently has a probability p_{ij} of achieving ACR50

$$r_{ij} \sim \text{Bi}(n_{ij}, p_{ij}) \tag{1}$$

α_i is the log odds of ACR50 in the control arm of study *i*, these are fixed effects, and are treated as nuisance parameters. θ_{ij} is the log odds ratio of ACR50 for study *i* treatment arm *j* given treatment with a biologic agent k_i compared to placebo.; and β the log odds ratio for treatment with MTX. These are assumed to act independently of each other, so the log odds ratio for the relevant biologic mono-therapy versus placebo is the same as for the relevant biologic combination therapy with MTX versus MTX. This is written

$$\begin{aligned} \text{logit}(p_{i0}) &= \log(p_{i0}/(1-p_{i0})) = \alpha_i + \beta m_{i0} \\ \text{logit}(p_{ij}) &= \alpha_i + \beta m_{ij} + \theta_{ij} \quad j = 1 \ldots J_i \end{aligned} \tag{2}$$

We assume each of these log odds ratios for biologic treatments have been sampled from a normal distribution. This is assuming all the treatment effects are exchangeable both between studies and within studies.

$$\theta_{ij} \sim \text{N}(\mu_{k_i}, \sigma^2) \tag{3}$$

σ^2 is the heterogeneity between treatments, assumed common for all treatments, and μ_k the overall log odds ratio of ACR50 given treatment with a biologic *k*. This is assuming all the treatment effects are exchangeable between treatment arms. We also assume equal heterogeneities between arms for treatment with every biologic agent. The model also allows for multiple treatment arms of the same drug within a study.

2.2.2. Model 2 - Mixed treatment comparison model with univariate random effects, including meta-regression coefficients

The average baseline disease duration and average baseline HAQ of patients are study level characteristics. In our second model, they are included as treatment-

disease duration and treatment-HAQ interaction effects to assess how they affect the log odds of ACR50 if treated compared to control. This is written:

$$\begin{aligned} \text{logit}(p_{i0}) &= \alpha_i + \beta m_{i0} \\ \text{logit}(p_{ij}) &= \alpha_i + \beta m_{ij} + \theta_{ij} + \gamma_1 x_{1i} + \gamma_2 x_{2i} \end{aligned} \quad (4)$$

This assumes that the β and γ parameters are the same for all treatments. In Model 2 therefore, the θ_{ij} have now been adjusted for study level covariates. Thus the θ_{ij} are interpreted as the log odds ratio for the relevant biologic therapy at the mean value of the study level covariates.

2.2.3. Model 3 – Mixed treatment comparison with bivariate random effects

The exchangeability assumption used on the random effects in model 1 and 2 is strong – the treatment effects both within a study and between studies are all exchangeable with each other. A further weakness is the effect of MTX is assumed to be the same in each study and it would be better to treat this in a similar way to treatment with a biologic, and allow these to be exchangeable between studies. This is written

$$\begin{aligned} \text{logit}(p_{i0}) &= \alpha_i + \beta_i m_{i0} \\ \text{logit}(p_{ij}) &= \alpha_i + \beta_i m_{ij} + \theta_i \quad j = 1 \ldots J_i \end{aligned} \quad (5)$$

We assume each of these log odds ratios has been sampled from a bivariate normal normal distribution. This is assuming all the treatment effects are exchangeable between studies. We also assume equal heterogeneities between studies for treatment with every biologic agent, treatment with MTX and the comparison between the two.

$$\begin{pmatrix} \beta_i \\ \theta_i \end{pmatrix} \sim BVN\left(\begin{pmatrix} \mu_\beta \\ \mu_{k_i} \end{pmatrix}, \sigma^2 \begin{pmatrix} 1 & 1/2 \\ 1/2 & 1 \end{pmatrix} \right) \quad (6)$$

σ^2 is the heterogeneity between studies, and μ_β and μ_{k_i} the overall log odds ratio of ACR50 given treatment with MTX and biologic *k* respectively.

The model also allows for multiple treatment arms of the same drug within a study, and assumes that treatment effects are the same for each arm within a study where the same treatment is used.

2.2.4. Model 4 - Mixed treatment comparison with bivariate random effects, including meta-regression coefficients

The average baseline disease duration and average baseline HAQ of patients are included in model 4 as meta-regression covariables in the same way as in model 2, and with the same random-effects structure as model 3:

$$\begin{aligned} \text{logit}(p_{i0}) &= \alpha_i + \beta_i m_{i0} \\ \text{logit}(p_{ij}) &= \alpha_i + \beta_i m_{ij} + \theta_i + \gamma_1 x_{1i} + \gamma_2 x_{2i} \end{aligned} \quad (7)$$

This assumes that the γ parameters are the same for all treatments, and β_i and θ_i have now been adjusted for study level covariates. Thus the θ_i are interpreted as the log odds ratio for the relevant biologic therapy at the mean value of the study level covariates.

2.2.5. Model 5 - Adding different random effects for TNF and IL-1 antagonists

Instead of assuming a different random effect mean for each drug type, a different random effect mean could be included for each drug class: TNF-$\propto$ antagonists and anakinra. In this model k_i denotes the biologic agent used in study *i,* where 1 indicates anakinra and 2 a TNF-$\propto$ antagonist. Model 4 is also fitted with this random effects construction to make an indirect comparison between anakinra and all TNF-$\propto$ antagonists.

2.2.6. Model fitting

All models are fitted by Markov chain Monte Carlo techniques (MCMC) (28). Using the computer package WinBUGS (29). Vague normal priors are placed on each α , μ , β , γ and δ ; and a vague positive uniform prior was placed on σ . All chains are run for 20 000 iterations after a burn in of 1000 iterations and demonstrated satisfactory convergence to their supporting posterior distributions. The code used to fit model 4 is given in the Appendix.

3. Results

The results of fitting the range of different models are shown in Table 2. This gives the median and the standard deviation of the posterior distribution of parameters, along with 95% credible intervals.

Models 1 and 3 are mixed treatment comparison models. Model 1 assumes exchangeability between trial arms (both within and between studies), and model 2 assumes exchangeability between studies, and also allows the MTX effect to vary between studies. They estimates the log odds ratio of an ACR50 event for treatment with each biologic and for MTX. They ignore the possible explanatory effects of mean disease duration and mean baseline HAQ disability in the studies. Both models suggest that anakinra and infliximab have comparable effectiveness, which is worse

than both etanercept and adalimumab. The estimates of the between-arm variability and between-study variability are 0.166 and 0.397 respectively.

Model 2 augments model 1, and model 4 augments model 3 by including study level characteristics of mean baseline disease duration and mean baseline HAQ. This has a substantial effect on the estimated log odds ratio of an ACR50 event. The three TNF-$\propto$ antagonists now appear to have comparable effectiveness, all better than anakinra. The between-study variability is now reduced to 0.065 and 0.036 and we see that including these study covariables accounts for $100\% \times (0.166 - 0.065)/0.166 =$ 61% of the between-arm heterogeneity and 91% of the between-study heterogeneity. The information used to estimate the MTX parameter β comes from situations where MTX is used in the control arm but not in the intervention arm, namely studies 6, 7 and 13. The possibility of an additional effect of a biologic if given in combination with MTX over and above the combined effect of the drugs given alone is estimated by including a biologic treatment-MTX interaction effect. This interaction effect is estimated as -0.518 and -0.485 from models 2 and 4 respectively with standard deviations of 0.341 and 0.364. Information for this interaction estimate is given where MTX is not always used in the treatment arm within a study, namely studies 7 and 13. As only two treatment arms supply information here it is not surprising this parameter is imprecisely estimated. The negative value means the combined effect of treatment and MTX is less than the sum of the effects of treatment and MTX given separately. However, as there is little information to estimate this parameter and the estimate of it is consistent with zero, we don't use this interaction parameter in the analysis.

There is very little difference in the inference from the meta-regression models 2 and 4, and we consider the assumption of study exchangeability of treatment effects of both biologic and MTX treatment, and common effects within studies to be a better assumption than between arm exchangeability on only the effect of biologics, which largely ignores the nested structure of the data. From now on we concern ourselves with describing the results from model 4.

The disease duration parameter is estimated as 0.119. This means that the *relative* effectiveness of biologic drugs versus the comparator is greater for studies with patients who have longer average duration since diagnosis with RA. Note the absolute effectiveness of biologics does not improve with longer mean disease duration. In fact, both the biologic and the comparator ACR50 scores fall with mean disease duration but that fall is much steeper for the comparator drugs. Thus, for every additional year of disease the expected odds ratio of an ACR50 event for a patient will be *exp*(0.119)=1.126 times larger. The 0.119 disease duration coefficient

is of a comparable order to the 0.112 gradient estimate from the linear regression (weighted by the variance of the log odds ratio) in Figure 1, which shows a plot of the observed log odds ratio of ACR50 at six months for all treatments plotted against the average disease duration for each study The HAQ parameter is estimated to be -1.616, so a study with higher average baseline HAQ is expected to show a log odds ratio which indicates worse relative effectivness. For every additional 0.1 baseline HAQ point the expected odds ratio of an ACR50 event will decrease by a factor of *exp*(-1.616*0.1)=0.851. Mean duration and baseline HAQ are correlated, so as the effects of these on the log odds ratio are in opposite directions they will to some extent cancel out for an average individual. The MTX parameter is estimated as 0.740. This means that the average patient responds better if MTX is given with the placebo or biologic drug. As, in this model, MTX-interaction does not influence the log odds of treatment, MTX affects the response equally in both the placebo and treatment arms. MTX increased the odds of an ACR50 response by a factor of *exp*(0.740)=2.096.

Figure 2 shows the observed log odds ratios of ACR50 at six months for each trial arm as solid dots, and the fitted log odds ratios from model 4 as open dots. These fitted values are estimated from the random effects, which have been shrunk towards the mean for that particular drug (30). This figure shows which trials did better or worse than expected once the disease duration, HAQ and MTX treatment have been accounted for. For example, 40 mg of adalimumab given weekly in the study by van de Putte did better than expected, whereas 100mg of anakinra given in combination with MTX daily in the study by Cohen 2001 did worse than expected.

Figure 3 shows how the predicted odds ratio of ACR50 at six months improves with the disease duration of the patient with average baseline HAQ, over all the studies, of $\bar{h}$ =1.557. All these predicted odds are from model 4 except for those pertaining to all TNF-$\propto$ antagonists, which are from model 5. The estimated mean log odds ratio of an ACR50 response given biologic treatment is given by

$$\mu_k + \mu_\beta m + \gamma_1(d - \bar{d}) + \gamma_2(h - \bar{h}) \qquad (8)$$

where μ_k is the random effects mean for the drug concerned, m takes the value 0 when estimating the log odds ratio for mono biologic therapy compared to placebo, or for biologic in combination with MTX compared to MTX; the value -1 for mono therapy compared to MTX and 1 for combination therapy compared to placeo. d is the disease duration, $\bar{d}$ =7.789 years is the average disease duration over all the studies and h is the baseline HAQ. This recentring is necessary as the disease duration and HAQ data are recentred in the model fitting. For example, the odds ratio of an ACR50 response for etanercept given to a patient with a disease duration of

three years and average baseline HAQ, compared to placebo is estimated by *exp*(1.437+0.119(3-7.789))=2.38. As the estimate of γ_1 is positive then all the drugs become more effective if used to treat patients with longer disease duration. The CI for the effectiveness of anakinra includes zero if this drug is used to treat RA patients with disease duration up to six years (for patients with average baseline HAQ). However, anakinra is effective at treating patients with longer disease duration. The TNF-$\propto$ antagonists as a class are effective at achieving ACR50 at six months for all disease durations (for patients with average baseline HAQ).

Figure 4 makes an indirect comparison of the odds ratio of ACR50 at six months for each pair of TNF-$\propto$ antagonists. This finds the odds ratio of ACR50 at six months when comparing each pair of TNF-$\propto$ antagonists. As $\mu_\beta m + \gamma_1(d-\bar{d}) + \gamma_2(h-\bar{h})$ is the same for any drug the difference in log odds ratios is modelled to be the same for any common disease duration, HAQ and MTX used in combination or as a comparator and is given by

$$\mu_{k1} - \mu_{k2} \tag{9}$$

where μ_{k1} and μ_{k2} are the random effect means for the numerator and denominator drugs respectively. For example, the odds ratio of ACR50 at six months if treated with infliximab compared to etanercept is *exp*(1.421-1.437)=0.98 95% CI (0.45,1.93).

4. Discussion

This is the first study, of which we are aware, to combine techniques of mixed treatment comparisons with meta-regression to adjust for study level covariables. Our case study, an important topic in the choice of treatments in Rheumatoid Arthritis, examined 13 randomised controlled trials that tested biologic treatments against comparator. No head to head studies of these therapies have been performed. Each of the trials measured ACR50 as an outcome and may have used the active comparator MTX in the control arm and in combination with the biologic therapy in the treatment arm. Additionally, the differences in study inclusion criteria meant disparity in the patient populations between the trials. Also these trials may have incorporated several treatment arms. We developed methods to deal with all these features. First, we used the techniques of mixed treatment comparisons by allowing different random effects for each biologic treatment in model 1 (where exchangeability is assumed between treatment arms), and also for treatment with MTX in model 3 (where exchangeability is assumed between studies). Second, ideas from meta-regression introduced study level covariables into models 2 and 4.

In terms of the specific case study, the results confirm the efficacy of TNF-∝ antagonists over control even for patients with very early disease. While each TNF-∝ antagonist has a slightly different mode of action or formulation, we found no statistical difference between their ability to induce an ACR50 response over placebo. We found that the expected effect of IL-1 antagonist anakinra is also superior to control for patients with disease duration greater than 6 years. However, less data are available for the anakinra estimate compared to TNF-∝ antagonist combined estimate so this leads to comparatively wider CI. This penalises anakinra, as longer disease duration is then necessary for the CI of the estimated effectiveness to exclude zero.

There are a number of potential limitations to the study. Models 1 and 2 assumed exchangeability between treatment arms (both within a study and between studies), and models 3 and 4 assumed exchangeability between studies. Models 3 and 4 also assume that the treatment effects are the same for each arm within a study where a particular treatment is used. This is reasonable for MTX, as the same dose is always used, however each arm of a study may use a different dose of the biologic drug. The model could be improved if some dose-response relationship were to be included in the model, but it is not clear how say 25mg of etanercept could be compared with 20mg of Adalimumab, nor even how 20mg of adalimumab administered every week should be compared with 40mg every other week. We do not explicitly account for the dose used within a treatment arm, but could extend model 4 to acknowledge that the treatment effects could be different for each arm, and make an exchangeability assumption on these within a study. The study level treatment effects are then also assumed to be exchangeable between studies.

$$
\begin{aligned}
&\text{logit}(p_{i0}) = \alpha_i + \beta_i m_{i0} \\
&\text{logit}(p_{ij}) = \alpha_i + \beta_i m_{ij} + \theta_{ij} + \gamma_1 x_{1i} + \gamma_2 x_{2i} \\
&\theta_{ij} \sim N(\theta_i, \sigma_w^2) \\
&\begin{pmatrix} \beta_i \\ \theta_i \end{pmatrix} \sim BVN\left(\begin{pmatrix} \mu_\beta \\ \mu_{k_i} \end{pmatrix}, \sigma^2 \begin{pmatrix} 1 & 1/2 \\ 1/2 & 1 \end{pmatrix} \right)
\end{aligned}
\qquad (10)
$$

σ_w^2 is the heterogeneity within studies and σ^2 the heterogeneity between studies. The meta-regression element of the model explains the between study heterogeneity and should reduce this, but does not affect the within study heterogeneity. However, we feel this model is allowing too much variability in the model, and an explicit dose response relationship would be better than the within study exchangeability assumption.

Secondly, we estimated β and μ_β from studies where MTX is used in the control but not in the intervention arm. Estimates of these parameters could have been improved by including trials of MTX vs. placebo, as these would have given a direct estimate of these parameters. We decided to restrict the meta-analysis to studies for biologic treatment, as most trials of MTX date back to an era before ACR50 measurement became the norm. We were also aware that the populations studied in these trials were often substantially different from the populations in our 13 studies.

Thirdly, an assumption of the models is that the study level parameters γ are the same for all treatments. This is probably a reasonable assumption for the TNF antagonists as they all have a similar mechanism of action, but maybe less reasonable for anakinra.

Fourthly, the relationship of six-month ACR50 with mean disease duration or with mean baseline HAQ of patients across trials may not be the same as these relationships for individual patients within trials (12). The relationship demonstrated here between the patient characteristics might be due to confounding with other study level variables that may not even have been measured, and there may or may not be a relationship between six-month ACR50 and disease duration or HAQ at a patient level. This is a generic problem with meta-regression and individual patient data is needed to find a relationship at this level. However, other studies have shown that disease duration and baseline HAQ are strong predictors of efficacy (26;27).

Lastly, we were not able to address the concern of publication bias, which could lead to a spuriously elevated risk estimate. This could potentially be relevant for anakinra, which has not reported the ACR results from its largest randomised study (31).

Models 3 and 4 are based on those from Lu and Ades (10), who, like us, compare multiple treatments for the same disease. They define a method for mixed treatment comparison where several trials are combined which test different treatments for the same disease and which measure the same outcome. The Lu and Ades method is used to strengthen the relative efficacy estimates that are directly measured in the trials and also to make indirect estimates of relative efficacies that are not directly measured. Multiple treatments being considered within a study require correlation between the treatment random effects as within-study treatment groups are correlated.

The models defined in this paper differ from those of Lu and Ades in a number of ways. The context of our RA example was that there were several treatment arms within a study all applying that same treatment. The control arm may be a placebo or

an active comparator, and the active comparator may also be used in combination with treatment, but possibly not for all treatment arms. Lu and Ades did not need to employ methods to account for these trial features. Furthermore, our methods also include meta-regression techniques so study level variables are used to try and explain the variability between studies, and the different doses between arms in a study are modelled.

An advantage with using MCMC to fit these models it that it allows credible interval to be sampled directly for statistics of interest, for example, the log odds ratio for a given disease duration and the difference between log odds ratios for different treatments. In this way all the correlations betweens the parameters that make up these statistics are dealt with appropriately. The models could have been fitted using classical techniques, although they may not fit into the pre-programmed routines of a package.

Until this analysis, it had been impossible to determine whether one TNF antagonist is superior to another. A direct randomised head to head study in the future is unlikely as there is no incentive for the existing pharmaceutical companies to fund such a study, and it would be difficult for a public body to justify the expense such a trial would consume. With the current evidence, we found no evidence to suspect that there are material differences between TNF-∝antagonists and on this evidence, claims that there are differences in efficacy must be considered with caution. There has been no formal analysis as yet of the value of information which might be provided from a head to head trial and given the analysis presented here, such a trial may not be the highest priority for further research. This does not mean that no further research is required. Sequential use of the TNF-∝therapies is becoming more common and long-term effectiveness and safety is being monitored by a number of registry studies.

In conclusion, this paper defines a methodology for combining meta-regression techniques with ideas from mixed treatment comparisons. This allows different treatments for the same condition to be compared whilst adjusting for difference in the study populations.

5. Appendix

5.1. Bugs data set

```
list(
N.c=13,
study.c=c(1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13),
mtx.c=c(1, 0, 1, 0, 1, 1, 1, 1, 1, 1, 1, 0, 1),
n.c=c(74, 121, 251, 80, 30, 217, 228, 88, 282, 62, 200, 110, 257),
r.acr.c=c(3, 10, 20, 4, 1, 67, 91, 8, 91, 5, 19, 9, 118),
N.t=33,
study.t=c(1, 1, 1, 1, 1, 2, 2, 2, 3, 4, 4, 5, 6, 6, 7, 7, 8, 8, 8, 8, 9, 9, 10, 10, 10, 11, 11, 12, 12, 12, 12, 13,
13),
mtx.t=c(1, 1, 1, 1, 1, 0, 0, 0, 1, 0, 0, 1, 0, 0, 1, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 0, 0, 0, 0, 0, 1),
n.t=c(63, 74, 77, 59, 72, 119, 116, 116, 250, 76, 78, 59, 207, 208, 231, 223, 86, 86, 87, 81, 359, 363,
69, 67, 73, 212, 207, 106, 112, 113, 103, 274, 268),
r.acr.t=c(8, 15, 8, 14, 12, 20, 13, 22, 43, 18, 31, 23, 80, 68, 133, 92, 19, 26, 35, 28, 164, 183, 22, 37, 31,
87, 81, 20, 23, 25, 36, 115, 163),
dur.s=c(7.45537, 4.023305, 10.74930, 11.99145, 13, 0.9670886, 6.63651, 10.58645, 0.864243,
12.33911, 10.96769, 10.93915, 0.7321652),
haq.b.s=c(1.404773, 1.549153, 1.349900, 1.666667, 1.5, 1.4, 1.766569, 1.720093, 1.5, 1.562952,
1.456931, 1.860294, 1.5),
drug.s=c(1, 1, 1, 2, 2, 2, 2, 3, 3, 4, 4, 4, 4)
)
```

5.2. Bugs code for model 4

```
model{
for(i in 1:N.c){
   r.acr.c[i] ~ dbin(p.c[i], n.c[i])
   logit(p.c[i]) <- mu[study.c[i]] + beta[study.c[i]]*mtx.c[i]
}

for(i in 1:N.t){
   r.acr.t[i] ~ dbin(p.t[i], n.t[i])
   logit(p.t[i]) <- mu[study.t[i]] + beta[study.t[i]]*mtx.t[i]+lor[i]
   lor[i] <- theta[study.t[i]]
             +gamma[1]*(dur.s[study.t[i]]-dur.s.bar)
              +gamma[2]*(haq.b.s[study.t[i]]-haq.b.s.bar)
   fit.lor[i]<-lor[i]+beta[study.t[i]]*(mtx.t[i]-mtx.c[study.t[i]]) #fitted log odds ratio
}

#random effect for all treatments
for(i in 1:N.c){
   theta[i] ~dnorm(theta.mean[i],tau)
   beta[i] ~ dnorm(beta.mean[i],tau.beta)
   theta.mean[i] <- mu.theta[drug.s[i]]  #drug.s is drug used in study i
   beta.mean[i] <- mu.beta+1/2*(theta[i]-theta.mean[i])
}
tau<-1/sigma.sq
sigma.sq<-sigma*sigma
tau.beta<-4/3*tau

#priors
for(i in 1:N.c){ mu[i] ~ dnorm(0, 1.0E-6)}
mu.beta~dnorm(0, 1.0E-6)
for(i in 1:4){mu.theta[i]~dnorm(0, 1.0E-6)}
```

```
sigma~dunif(0,2)

gamma[1] ~ dnorm(0, 1.0E-6)      # duration
gamma[2] ~ dnorm(0, 1.0E-6)      # haq

#transformed variables
for(i in 1:4){exp.mu.theta[i]<-exp(mu.theta[i])}

#adjusted mean lor for various durations and treated with MTX and anti-TNF.
average rf and haq.
for(t in 1:4){
   for(d in 1:16){
      adj.lor[d,t]<-mu.theta[t]+gamma[1]*(d-1-dur.s.bar)
        adj.or[d,t]<-exp(adj.lor[d,t])
   }
}

#difference in log OR between treatments. first-second
for(i in 1:3){
   i1[i]<-study.c[i]+1
   for(j in (i+1):4){
      df.lor[j,i]<-mu.theta[j]-mu.theta[i]
      df.or[j,i]<-exp(df.lor[j,i])
   }
}

#OR for combination therapy at mean baseline characteristics
for(i in 1:4){
   mu.theta.mtx[i]<-mu.theta[i]+mu.beta
   exp.mu.theta.mtx[i]<-exp(mu.theta.mtx[i])
}

#extra variables
dur.s.bar<-mean(dur.s[])
haq.b.s.bar<-mean(haq.b.s[])

}
```

Tables and figures

Table 1 Data extracted from included phase three studies

Table 2 Parameter estimates for models 1 to 5.

Figure 1 Observed log odds ratio of ACR50 at six months in all treatment arms of studies compared to the control arm, by average disease duration. The linear regression weighted by the inverse of the variance of the log odds ratio estimate is also shown. The area of each circle is inversely proportional to the variance of the log odds ratio estimate and the shading of the circle relates to the treatment used. The disease duration is the same for all arms within a study, and the study relating to the "column" of disease duration circles is given in the margin above the plot.

Figure 2 Plot of observed and fitted log odds ratios from model 4.

Figure 3 Odds ratio of ACR50 by treatment and disease duration compared to control predicted from model 4 and 5.

Figure 4 Odds ratios of ACR50 for all TNF-$\propto$ antagonist treatment pairs predicted from model 4. The Odds ratios and 95% CI are also shown.

Table 1

Study	Trial	Mean Baseline Characteristics			Intervention	N	ACR50 at 6 Months
		Age (years)	Disease duration (years)	Baseline HAQ			
1	Cohen 2002 (18)	53	7.5	1.4	Placebo + MTX	74	4%
					Anakinra 0.04mg/kg/day + MTX	63	13%
					Anakinra 0.1mg/kg/day + MTX	74	20%
					Anakinra 0.4mg/kg/day + MTX	77	10%
					Anakinra 1.0mg/kg/day + MTX	59	24%
					Anakinra 2.0mg/kg/day + MTX	72	17%
2	Bresnihan 1998 (17)	53	4.0	1.5	Placebo	121	8%
					Anakinra 30mg/day	119	17%
					Anakinra 75mg/day	116	11%
					Anakinra 150mg/day	116	19%
3	Cohen 2004 (19)	57	10.7	1.3	Placebo+ MTX	251	8%
					Anakinra 100mg/day + MTX	250	17%
4	Moreland 1999 (22)	52	12.0	1.7	Placebo	80	5%
					Etanercept 10mg 2xweek	76	24%
					Etanercept 25mg 2xweek	78	40%
5	Weinblatt 1999 (23)	50	13.0	1.5	Placebo + MTX	30	3%
					Etanercept 25mg 2xweek + MTX	59	39%
6	ERA 2000 (20)	50	1.0	1.4	Placebo + MTX	217	31%
					Etanercept 25mg 2xweek	207	39%
					Etanercept 10mg 2xweek	208	33%
7	TEMPO 2004 (21)	53	6.6	1.8	Placebo + MTX	228	40%
					Etanercept 25mg 2xweek + MTX	231	58%
					Etanercept 25mg 2xweek	223	41%
8	ATTRACT 1999 (25)	53	10.6	1.7	Placebo + MTX	88	9%
					Infliximab 3mg/kg q8wks + MTX	86	22%
					Infliximab 3mg/kg q4wks + MTX	86	30%
					Infliximab 10mg/kg q8wks + MTX	87	40%
					Infliximab 10mg/kg q4wks + MTX	81	35%
9	ASPIRE 2004 (24)	50	0.9	1.5	MTX	282	32%*
					Infliximab 3mg/kg q8wks + MTX	359	46%*
					Infliximab 6mg/kg q8wks+ MTX	363	50%*
10	ARMADA 2003 (16)	56	12.3	1.6	Placebo + MTX	62	8%
					Adalimumab 20mg eow + MTX	69	32%
					Adalimumab 40mg eow + MTX	67	55%
					Adalimumab 60mg eow + MTX	73	42%
11	Keystone 2004 (14)	57	11.0	1.5	Placebo + MTX	200	10%
					Adalimumab 20mg eow + MTX	212	41%
					Adalimumab 40mg eow + MTX	207	39%
12	van de Putte 2004 (15)	47	10.9	1.9	Placebo	110	8%
					Adalimumab 20mg eow	106	19%
					Adalimumab 20mg wkl	112	21%
					Adalimumab 40mg eow	113	22%
					Adalimumab 40mg wkl	103	35%
13	PREMIER 2005(13)	52	0.7	1.5	MTX	257	46%*
					Adalimumab 40mg eow	274	42%*
					Adalimumab 40mg eow + MTX	268	61%*

* indicates the ACR50 at six months has been estimated by the ACR50 at 12 months.
eow=every other week, wkl=weekly.

Table 2

Model	Description	Parameter	Median	SD	95% CI	
1	Anakinra	μ_1	0.983	0.289	(0.432	1.562)
	Etanercept	μ_2	1.573	0.292	(1.041	2.194)
	Infliximab	μ_3	0.991	0.262	(0.514	1.538)
	Adalimumab	μ_4	1.441	0.210	(1.045	1.871)
	MTX	β	1.438	0.320	(0.851	2.120)
	Between arm variance	σ^2	0.166	0.083	(0.066	0.382)
2	Anakinra	μ_1	0.805	0.253	(0.337	1.334)
	Etanercept	μ_2	1.468	0.238	(1.025	1.963)
	Infliximab	μ_3	1.398	0.232	(0.957	1.868)
	Adalimumab	μ_4	1.385	0.173	(1.058	1.738)
	MTX	β	0.798	0.267	(0.286	1.347)
	Baseline disease duration	γ_1	0.116	0.026	(0.065	0.169)
	Baseline HAQ	γ_1	-1.669	0.781	(-3.199	-0.090)
	Between arm variance	σ^2	0.065	0.049	0.009	0.196
3	Anakinra	μ_1	1.025	0.4737	(0.107	2.009)
	Etanercept	μ_2	1.544	0.4298	(0.741	2.450)
	Infliximab	μ_3	1.047	0.5427	(-0.00184	2.182)
	Adalimumab	μ_4	1.419	0.3765	(0.701	2.196)
	MTX	μ_β	1.177	0.4245	(0.284	2.020)
	Between study variance	σ^2	0.397	0.374	(0.100	1.505)
4	Anakinra	μ_1	0.758	0.300	(0.237	1.440)
	Etanercept	μ_2	1.437	0.253	(1.008	2.006)
	Infliximab	μ_3	1.421	0.284	(0.881	2.009)
	Adalimumab	μ_4	1.380	0.199	(1.005	1.804)
	MTX	μ_β	0.740	0.218	(0.359	1.207)
	Baseline disease duration	γ_1	0.119	0.0279	(0.0647	0.175)
	Baseline HAQ	γ_1	-1.616	0.884	(-3.225	0.344)
	Between study variance	σ^2	0.036	0.126	(0.000	0.404)
5	Anakinra	μ_1	0.740	0.260	(0.284	1.277)
	TNF antagonist	μ_2	1.404	0.127	(1.154	1.653)
	MTX	μ_β	0.735	0.163	(0.416	1.061)
	Baseline disease duration	γ_1	0.117	0.023	(0.074	0.164)
	Baseline HAQ	γ_1	-1.634	0.752	(-3.055	-0.084)
	Between study variance	σ^2	0.014	0.056	(0.000	0.190)

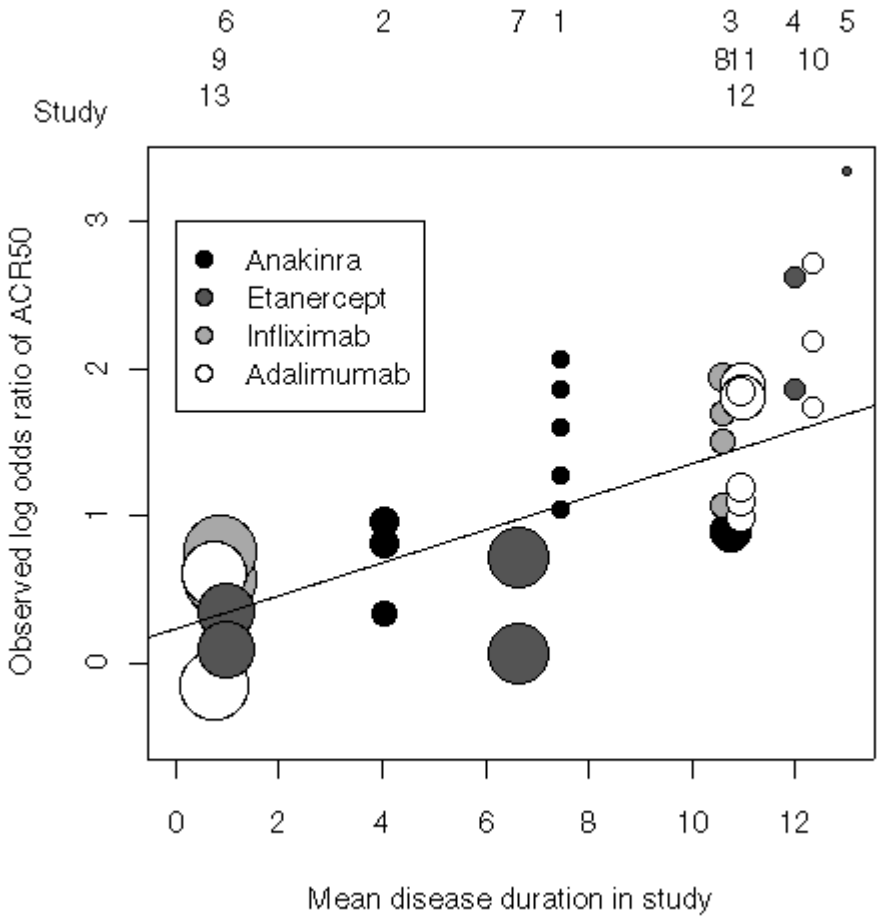
Study
6
9
13
2
7
1
3
8
11
12
4
10
5
Anakinra
Etanercept
Infliximab
Adalimumab
Observed log odds ratio of ACR50
0
1
2
3
0
2
4
6
8
10
12
Mean disease duration in study

Figure 1

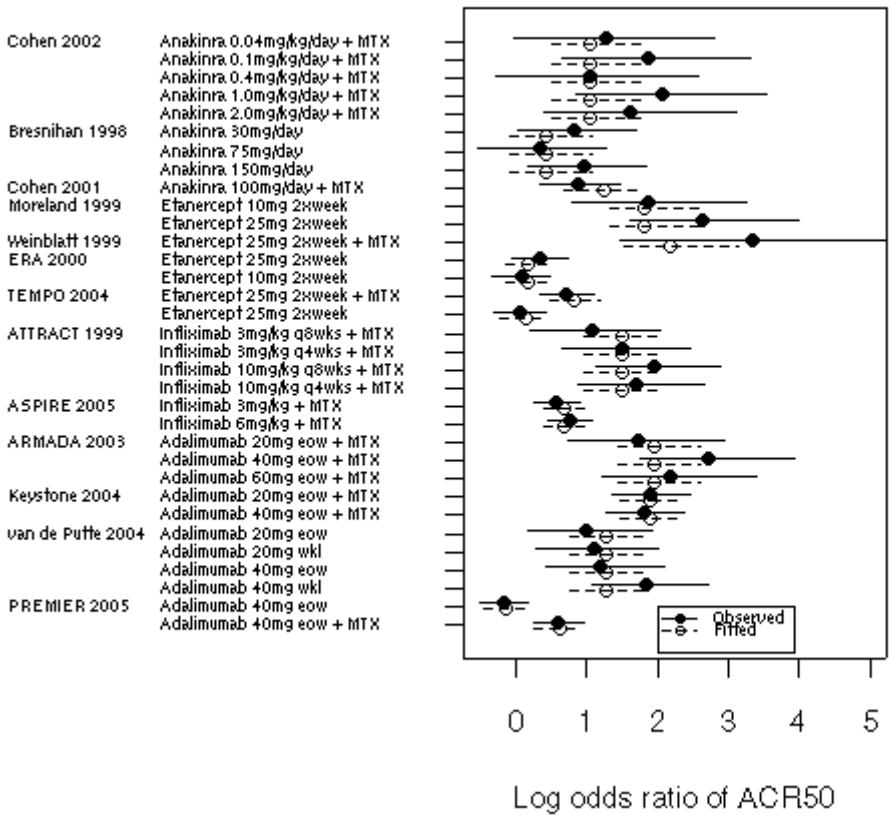
Cohen 2002
Anakinra 0.04mg/kg/day + MTX
Anakinra 0.1mg/kg/day + MTX
Anakinra 0.4mg/kg/day + MTX
Anakinra 1.0mg/kg/day + MTX
Anakinra 2.0mg/kg/day + MTX
Bresnihan 1998
Anakinra 30mg/day
Anakinra 75mg/day
Anakinra 150mg/day
Cohen 2001
Anakinra 100mg/day + MTX
Moreland 1999
Etanercept 10mg 2xweek
Etanercept 25mg 2xweek
Weinblatt 1999
Etanercept 25mg 2xweek + MTX
ERA 2000
Etanercept 25mg 2xweek
Etanercept 10mg 2xweek
TEMPO 2004
Etanercept 25mg 2xweek + MTX
Etanercept 25mg 2xweek
ATTRACT 1999
Infliximab 3mg/kg q8wks + MTX
Infliximab 3mg/kg q4wks + MTX
Infliximab 10mg/kg q8wks + MTX
Infliximab 10mg/kg q4wks + MTX
ASPIRE 2005
Infliximab 3mg/kg + MTX
Infliximab 6mg/kg + MTX
ARMADA 2003
Adalimumab 20mg eow + MTX
Adalimumab 40mg eow + MTX
Adalimumab 60mg eow + MTX
Keystone 2004
Adalimumab 20mg eow + MTX
Adalimumab 40mg eow + MTX
van de Putte 2004
Adalimumab 20mg eow
Adalimumab 20mg wkl
Adalimumab 40mg eow
Adalimumab 40mg wkl
PREMIER 2005
Adalimumab 40mg eow
Adalimumab 40mg eow + MTX
Observed
Fitted
0
1
2
3
4
5
Log odds ratio of ACR50

Figure 2

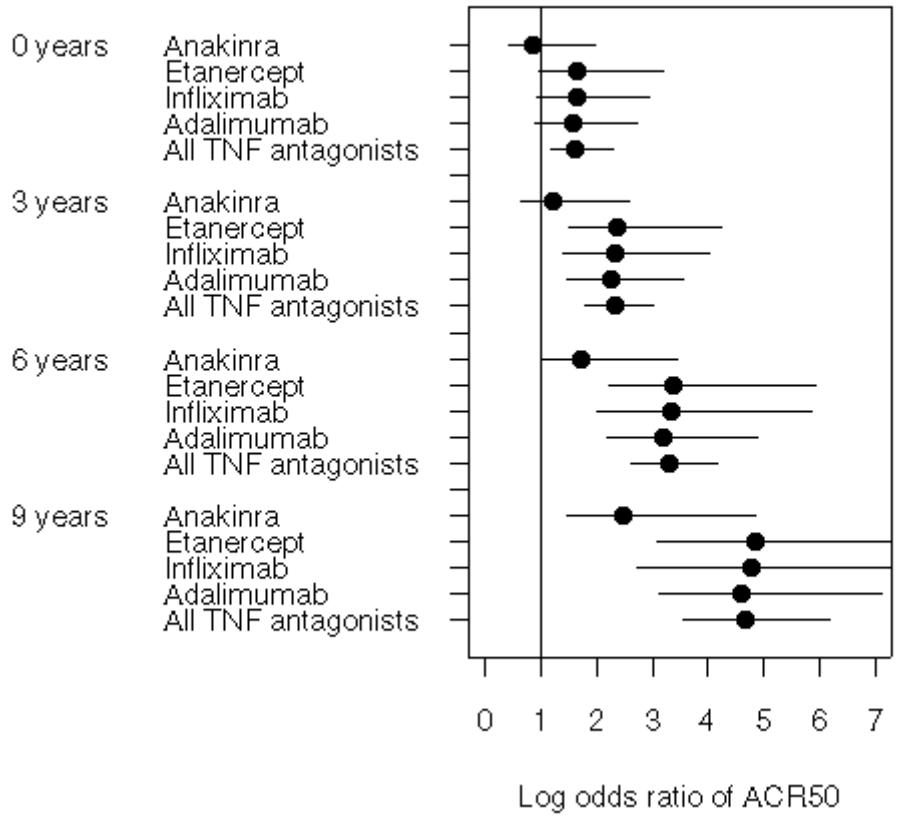
0 years
Anakinra
Etanercept
Infliximab
Adalimumab
All TNF antagonists
3 years
Anakinra
Etanercept
Infliximab
Adalimumab
All TNF antagonists
6 years
Anakinra
Etanercept
Infliximab
Adalimumab
All TNF antagonists
9 years
Anakinra
Etanercept
Infliximab
Adalimumab
All TNF antagonists
0 1 2 3 4 5 6 7
Log odds ratio of ACR50

Figure 3

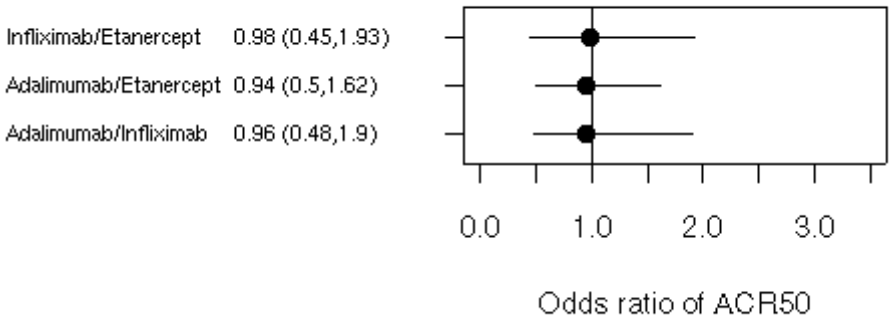
Infliximab/Etanercept 0.98 (0.45,1.93)
Adalimumab/Etanercept 0.94 (0.5,1.62)
Adalimumab/Infliximab 0.96 (0.48,1.9)
0.0
1.0
2.0
3.0
Odds ratio of ACR50

Figure 4

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