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Indirect Treatment Comparison in Meta-Analysis Using Three Methods for Rheumatoid Arthritis

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Abstract

Background: *The data were extracted from the comparative effectiveness review (CER) on pharmacological treatments for rheumatoid arthritis (RA) developed by the International University of North Carolina Evidence Based Practice Center (UNC EPC). The included studies enrolled patients with active RA despite oral disease-modifying antirheumatic drugs (DMARD) therapy. The outcome measures of choice were American College of Rheumatology (ACR) 20/50/70 response rates.*

Objective: *To compare and find the best treatment for RA among Adalimumab (Drug A), Infliximab (Drug B) and Certolizumab (Drug C) by using three different methods of indirect treatment comparison (ITC) in meta-analysis.*

Methods: *Three different methods of ITC were used. They were—Bucher, a simplest method which compares two treatments through a single common comparator; Lumley, the network comparison which compares two treatments through more than one common comparator or linking treatment; and the Confidence Profile method which compares two treatments through many comparators by using Bayesian technique.*

Results: *The Odds ratio obtained from Bucher ITC was* OR_{AC} *=0.417 (CI: 0.282 to 0.610) and* OR_{BC} *=0.334 (CI: 0.226 to 0.495); Lumley's OR was* OR_{AC} *=0.327 (CI: 0.0041, 26) and* OR_{BC} *=0.342 (CI: 0.0043, 27.15). By using Confidence Profile method,* OR_{AC} *=0.369 (CI: 0.204, 0.76) and* OR_{BC} *=0.305 (CI: 0.164, 0.636). The Odds ratio obtained from all the three methods was similar, concluding that Certolizumab is better as compared to Adalimumab and Infliximab.*

Conclusion: *Certolizumab is the best treatment for RA among various treatments.*

Keywords: *rheumatoid arthritis (RA), meta-analysis, indirect treatment comparison, Bayesian method, odds ratio*

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INTRODUCTION

Over the last few years, the themes of evidence reviews, evidence-based healthcare, systematic reviews and meta-analysis which occur and re-occur in several countries, academic disciplines and policy areas have started to converge. An example of this is the development of an international collaboration—the Campbell Collaboration—which will prepare and maintain systematic reviews of research on the effects of interventions in areas such as education, criminal justice, social policy and social care [1, 2]. Today meta-analysis has become a key component of evidence-based medicine. Meta-analysis is also becoming widely applied beyond randomized clinical trials; for example in epidemiological research. Goodman (1998) hails meta-analysis as "*one of the most important and controversial development in the history of science"* [3, 4].

Direct comparisons provide more reliable information about how two medicines compare. Such trials do not always happen before a medicine is approved and made available—at this point; many medicines have been compared with placebo, but not with other medicines [5–8]. Indirect treatment comparison refers to a comparison of different healthcare interventions using data from separate studies, in contrast to a direct comparison within randomized controlled trials. Indirect comparison is often used

because of a lack of, or insufficient evidence from head-to-head comparative trials [9–12].

Bayes theorem, named after an 18th century English clergyman. Bayesian statisticians express their belief about the size of an effect by specifying some prior probability distribution before seeing the data, and then they update that belief by deriving a posterior probability distribution, taking the data into account. Bayesian approaches are controversial because the definition of prior probability will often be based on subjective assessments and opinion [13].

$$P(\theta|\text{data}) \propto P(\text{data}|\theta) \times P(\theta).$$

The posterior density function is obtained by multiplying the prior density by the likelihood function.

RHEUMATOID ARTHRITIS (RA)

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. It can affect multiple other organs of the body; RA is referred to as a systemic illness and is sometimes called rheumatoid disease [14–16]. Its incidence and prevalence is more in developed countries and less in developing countries except India. In India the prevalence of RA is 0.75% which is similar to that in the West [17].

OBJECTIVE

There were many treatments that were included in the study, but the main interest was to compare treatments such as Adalimumab, Infliximab and Certolizumab as these three treatments were considered to be some of the 'better' treatments for treating RA.

Study Selection

The International University of North Carolina Evidence-based Practice Center (UNC EPC) developed the comparative effectiveness review (CER) on pharmacological treatments for RA. Sources were searched from the National Library of Medicine (NLM) publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses from June 2006 to March 2010.

Data Synthesis

The outcome measures of choice were American College of Rheumatology (ACR) 20/50/70 response rates and withdrawals (overall, due to lack of efficacy, and due to adverse events). Also the treatments in each study were considered to have binary outcome measures.

Bucher Indirect Treatment Comparison

This method was proposed by Bucher *et al*., in 1997. This is the simplest among all the three methods. The treatments compared Adalimumab versus Certolizumab and Infliximab versus Certolizumab by using a common comparator called Placebo + Methotrexate.

$\ln OR_{AC} = \ln OR_{AP} - \ln OR_{CP}$; $Var_{AC} = Var_{AP} + Var_{CP}$

The standard error is estimated from the above variance to substitute it in the confidence interval formula i.e., CI = $\ln OR \pm (1.96 * SE)$. Exponential for the ln value and for the obtained confidence interval was taken. The same procedure was followed for the other treatment comparison also.

Assumptions:

1. The principal assumption of the model proposed by Bucher *et al.* is that the relative efficacy of a treatment is the same in all trials included in the indirect comparison.
2. This method assumes independence between pair-wise comparisons, which is not found in three-arm trials.

Lumley Network Meta-analysis for Indirect Treatment Comparison

Network meta-analysis allows determining the amount of agreement between the results obtained when different linking treatments are used. Lumley has indicated that if the indirect comparison yields the same results, regardless of common comparator, then there is a greater likelihood that the ITC represents the true relationship between the interventions. If there is a discrepancy then ***"incoherence"*** exists and Lumley has provided mechanisms to measure this incoherence. The network meta-analytic approach may be of interest exists when an indirect comparison between two treatments can occur through *"multiple paths",* which requires indirect comparisons within indirect comparisons.

The formal model for the network comparison is,

$$Y_{ijk} \sim N(\mu_i - \mu_j + \eta_{ik} + \eta_{jk} + \xi_{ij}, \sigma^2_{ijk})$$

$$\eta_{ij} \sim N(0, \tau^2)$$

$$\xi_{ij} \sim N(0, \omega^2)$$

where:

Y_{ijk} is the treatment difference estimate from the kth RCT comparing treatment i and j;

σ^2_{ijk} is the standard deviation error of Y_{ijk};

μ_i is the average effect of treatment i;

η_{ik} is a random effect with variance τ^2 representing the difference between the average effects of treatment i and j;

ξ_{ij} is a random effect with variance ω^2 representing a change in the effect of treatment i when it is compared to treatment j.

It should be noted that,

η_{ik} random effects capture the heterogeneity of treatment effect.

ξ_{ij} random effects capture the inconsistency of pairs of treatments.

ω^2 is the incoherence of the network.

The formula for SE is,

Se = sqrt((sedrug12+sedrug2**2-2*corr*sedrug1*sedrug2))**

The correlation matrix for the treatment comparison obtained by using R software was zero for Drug A versus Drug C and Drug B versus Drug C.

$\ln OR_{AC} = \ln OR_{AP} - \ln OR_{CP}$ and the confidence interval was obtained by substituting the standard error in the CI formula, i.e. CI = $\ln OR \pm (1.96 * SE)$.

Assumptions:

1. The basic assumption underlying in the network meta-analysis is that the comparison between two interventions will occur through a closed loop.
2. A closed loop design is necessary for calculating the estimate of ***"incoherence,"*** which is then used to construct a 95% confidence interval for the indirect estimate.
3. Pathways that follow a star design or a ladder design cannot be used in the network meta- analysis. Such designs cannot quantify the amount of incoherence in a network of comparisons.

MODELS FOR MULTI-PARAMETER SYNTHESIS AND CONSISTENCY OF EVIDENCE

The confidence profile method (CPM) is a category of techniques used to conduct both direct and indirect treatment comparisons. Analyses conducted in the CPM are based on Bayesian inference. When a result for a parameter of interest is obtained, it presents itself in the form of a distribution, rather than a point estimate. Additionally, before actual data are used to obtain information about a parameter, a mathematical model is constructed and includes a term to quantify prior knowledge about the parameter of interest. Within the CPM structure, two techniques have been generated for the indirect evidence—1. Intermediate outcomes; 2. Technology families.

Intermediate Outcomes

This method is used to compare two treatments on clinical end points but it relates the effect of treatment to intermediate endpoints or surrogate outcomes and the effect of those intermediate endpoints to clinical outcomes. The parameter of interest is the combination of both posterior distributions.

Technology Families

This method is used to compare two treatments, referred to as technologies, which

are not compared directly. Eddy *et al*., developed a formula to combine the posterior distributions that are generated when each treatment is compared to the control. Ades extended random and fixed models in order that may be used to combine direct and indirect evidence. Three model-checking statistics were generated to determine the goodness of fit of each model, namely:

1) The posterior mean deviance pD, which measures model fit for each parameter estimated in the model, and values greater than 1 indicate that the model fits the parameter poorly.
2) Posterior predictive value p(ext)%, which represents the probability of obtaining a more extreme result than that which is observed.
3) The conditional predictive ordinate (CPO), which indicates the probability of the observed result while considering the model and the rest of the data.

Influence Diagram for an Indirect Comparison Using the Confidence Profile Method

The model for Confidence Profile method is,

$$\log it(P_{it}) = \mu_{ib} + \delta_{ib}$$

where,

P_{it} is the probability of the event for treatment t in trial i;

μ_{ib} is the log odds of the event for the reference treatment 'b' in trial i;

δ_{ib} is the trial-specific log odds ratio of the treatment 't' relative to the reference treatment b;

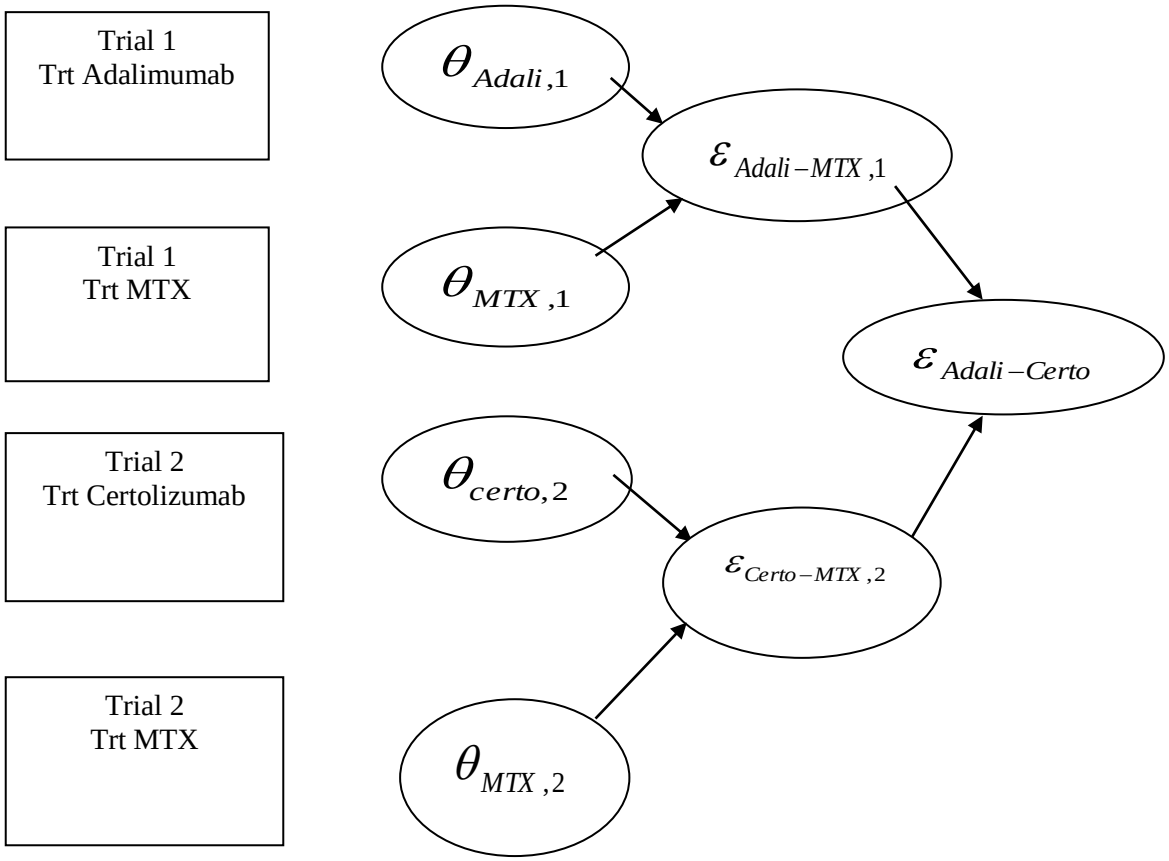
$$\delta_{ib} \sim dnorm(d_{bt}, \tau_i)$$

d_{bt} is the mean of the distribution;

τ_i is the precision of the log odds ratio of the distribution and

$$\tau = {}^{1}\!/_{pow(sd,2)}$$

$$sd \sim dunif(0,2)$$



The above is the vague prior for random effects of standard deviation.

The model of our dataset is,

$\log it(P_{it}) = \mu_{ib} + \delta_{ib}$

where,

P_{it} is the probability of the event for Adalimumab in trial 'i';

μ_{ib} is the log odds of the event for the reference treatment 'placebo + MTX' in trial 'i'.

δ_{ib} is the trial specific log odds ratio of the treatment 'Adali' relative to the reference treatment 'placebo + MTX'.

Similarly the model was fitted for other treatments which are included in the study.

Assumptions: A primary assumption underlying both models is that it is valid to combine the different sources of data that have been selected for the indirect comparison.

a) For the analysis of intermediate outcomes, the method proposed by Eddy *et al*., and further extended by Ades, assumes that a clinical and causal relationship exists between the surrogate and clinical endpoints.
b) The cross-validatory predictive checking method for evidence consistency requires the availability of direct evidence and can only determine whether or not the indirect sources of data can be validly combined with direct evidence.

RESULTS

Three different software for the three methods of indirect treatment comparison were used. a) STATA for Bucher Indirect Treatment Comparison, b) SAS for Lumley Network Comparison method, and c) WINBUGS for Confidence Profile method (Table 1).

Table 1: *Comparison of all the Three Methods.*

Treatment of comparison	Bucher ITC (STATA)	Lumley ITC (SAS)	CPM (WINBUGS)
Adalimumab *vs.* Certolizumab	OR=0.4147 CI=0.282, 0.610	OR=0.327 CI=0.0041, 26	OR=0.369 CI=0.204, 0.76
Infliximab *vs.* Certolizumab	OR=0.334 CI=0.226, 0.495	OR=0.342 CI=0.0043, 27.15	OR=0.305 CI=0.164, 0.636

The conclusion drawn from Table 1 was that the Odds ratio obtained from all the three methods were similar saying that Certolizumab was more effective as compared to Drug A and Drug B for treating RA.

DISCUSSION

Methodological problems in using indirect comparison:

a. Unclear understanding of underlying assumptions.
b. Incomplete search and inclusion of relevant studies.
c. Use of flawed or inappropriate methods.
d. Lack of objective and validated methods to assess or improve trial similarity.
e. Inadequate comparison and inappropriate combination of direct and indirect evidence.
f. The naive indirect comparison is methodologically flawed because the strength of randomization is totally disregarded.

RECOMMENDATIONS

i) More explicit and elaborate description and discussion of underlying assumptions in methodological studies and in systematic reviews in which different interventions are indirectly compared.
ii) Literature search needs to be systematic in order to identify all relevant studies.
iii) The availability of all active treatment controlled studies that are suitable for adjusted indirect comparison should be explicitly discussed, and justifications provided if only placebo controlled trials are used for adjusted indirect comparison.
iv) Data from trials with multiple arms should be appropriately analyzed, to avoid both downgrading direct evidence and using the same control group more than once in adjusted indirect comparison.

SUMMARY AND CONCLUSION

The aim of this study was to find the best treatment for treating RA. The outcome of interest was Odds ratio and it was calculated in all the three methods. The Odds ratio obtained from all the three methods of indirect treatment comparison of meta-analysis given in the results were more similar saying that *"Certolizumab"* is the best one among all the treatments, for treating RA.

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