Risk of Serious Adverse Effects and Death Associated with Biological and Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs in Patients with Rheumatoid Arthritis: *Protocol for a Systematic Review and Meta-analysis of Randomized Controlled Trials*

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Conflicts of interest

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Steffen Thirstrup, works as a regulatory consultant at NDA Regulatory Services Ltd, but does not receive fees directly from pharmaceutical companies

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Review methods

Review question

To evaluate and compare risk of serious adverse effects and death associated with treatment with currently approved biological and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) in adults with Rheumatoid Arthritis (RA) based on data from randomized controlled trials (RCTs). Robustness of the results will be evaluated by implications of using various statistical meta-analytical methods. We will explore whether an apparent safety signal is influenced by whether the study is using an adaptive trial design or not.

Searches

We will search the following bibliographic databases: The Cochrane Central Register of Controlled Trials (the Cochrane Library, latest issue), MEDLINE via PubMed (from 1950), and EMBASE via Ovid (from 1980), by applying search strategies developed by Dossing et al (1). Reference lists from relevant systematic reviews and RCTs will be hand-searched for additional citations not retrieved through electronic databases. Additionally, we will search clinicaltrials.gov using the following search: Study Type (Interventional); Conditions (rheumatoid arthritis); Interventions (abatacept OR 188667 OR CTLA4Ig OR adalimumab OR D2E7 OR anakinra OR certolizumab OR CDP870 OR etanercept OR TNFR:Fc OR golimumab OR CNTO148 OR infliximab OR rituximab OR tocilizumab OR tofacitinib OR CP-690,550). FDA, EMA, and b/tsDMARD marketing authorisation holder pharmaceutical company's online databases will be scrutinized to identify unpublished trial data. Finally, electronic abstract databases of the annual scientific meetings of both the 'American College of Rheumatology' (ACR) and the 'European League Against Rheumatism' (EULAR) will be searched via Web of Science to identify unpublished trial data using the following search: (TITLE:(rheumatoid) AND TITLE:(cimzia OR simponi OR rituxan OR orencia OR CTLA4Ig OR kineret OR humira OR enbrel OR remicade OR TNFR:Fc OR abatacept OR 188667 OR adalimumab OR D2E7 OR anakinra OR certolizumab OR CDP870 OR etanercept OR golimumab OR CNTO 148 OR infliximab OR rituximab OR tocilizumab OR tofacitinib OR CP-690,550 OR Xeljanz); Refined by: DOCUMENT TYPES:(MEETING ABSTRACT) AND SOURCE TITLES: (ARTHRITIS AND RHEUMATISM OR

ANNALS OF THE RHEUMATIC DISEASES). Throughout there will be no language restrictions on the systematic search approach.

Condition or domain being studied

Contemporary therapy for RA focuses on suppressing inflammation as early as possible (2) by pharmacological therapy including conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). Unlike csDMARDs the bDMARDs and tsDMARDs (b/tsDMARDs) have more specific immunological targets. Increasing evidence has accumulated on the efficacy and clinical use of b/tsDMARDs for the treatment of RA. Adverse effects, however, will remain (3;4). The appropriate use of pharmacological therapy requires doctors experienced in the diagnosis, treatment, and assessment of RA, who are skilled in the observations of efficacy and toxicity. Because b/tsDMARDs have adverse effects (5;6), patients or their representatives should be provided with information about potential risks and benefits in order that they may give informed consent for treatment. The approval of b/tsDMARDs has been based on the ability of the drugs to achieve clinical response relative to placebo, with the studies not being adequately powered to determine the potential harmful effects of these drugs. For adverse outcomes, meta-analysis may be the only way to obtain reliable evidence of potential harmful effect of these drugs. Although there is considerable debate regarding using RCTs as opposed to observational data in systematic reviews of adverse effects (7), empirical evidence indicates that there is no difference on the risk estimate of adverse effects derived from meta-analyses of RCTs and meta-analyses of observational studies (8). For this review, we will only include RCTs. However, long-term observational studies, including population-based registries, can provide realistic longer-term estimates of the risks of b/tsDMARDs, although they too have their limitations (8). There is now several meta-analyses evaluating different aspect of safety of bDMARDS for the treatment of RA (9-18). Some of them use a pairwise meta-analysis approach and some use an indirect and multiple treatment comparison meta-analysis approach. Further, many of these arrive at different conclusions about each bDMARD relative to placebo or indirectly compared in terms of various safety aspects. Such inconsistencies make it difficult for clinicians and policy makers when prioritising among the available b/tsDMARDs which to some extend seems to be comparable in terms of efficacy (19). One of the key limitations of these meta-

analyses might be issues related to the “adaptive trial design” in some analysed RCTs - often leading to high dropout rate in the control arm which may influence the observable adverse event rate when compared to the intervention. This factor is only explored to some extend in one study and only in a subgroup of the available b/tsDMARDs, and only in relation to placebo (18). We will attempt to adjust for the skewed dropout when evaluating important safety aspects of all Food and Drug Administration (FDA) or European Medicines Agency (EMA) approved b/tsDMARDs for RA.

Participants

We will study adults (≥18 years of age) with a diagnosis of RA, using the well-established clinical definition of the American College of Rheumatology (ACR) criteria(20) or equivalent.

Interventions

The 10 drugs included are in alphabetical order: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, tofacitinib applied in EMA/FDA approved administration form(s), either as add-on treatment to csDMARD(s) (e.g. MTX) or without concomitant allocated treatment. Combination therapy of more than one b/tsDMARD will not be considered eligible in accordance with their product label.

Comparators

Control interventions will include non-b/tsDMARD interventions, either csDMARD(s) or allocation to a non-treatment control (e.g. placebo or continued background therapy). Further, any of above defined b/tsDMARD interventions will also be eligible as comparators in order to include direct evidence from contrasts between 2 different b/tsDMARDs or between the same b/tsDMARD with and without csDMARD(s).

Types of study to be included

We will include both open-label and blinded RCTs with parallel group designs. Study participants had to be randomized to receive treatment with:

- $b/tsDMARD_{(i)}$ + csDMARD(s) vs. no-b/tsDMARD + csDMARD(s)

- b/tsDMARD $_{(i)}$ without csDMARD(s) vs. no-b/tsDMARD without csDMARD(s)
- b/tsDMARD $_{(i)}$ without csDMARD(s) vs. no-b/tsDMARD + csDMARD(s)
- b/tsDMARD $_{(i)}$ without csDMARD(s) vs. b/tsDMARD $_{(i)}$ + csDMARD(s)
- b/tsDMARD $_{(i)}$ + csDMARD(s) vs. b/tsDMARD $_{(ii)}$ + csDMARD(s)
- b/tsDMARD $_{(i)}$ without csDMARD(s) vs. b/tsDMARD $_{(ii)}$ without csDMARD(s)

RCTs evaluating single dose administration will not be consider eligible e.g. pharmacokinetic studies.

Co-Primary outcome

- Serious adverse effects, evaluated with number of patients experiencing at least one serious adverse event (SAE), (without distinguishing between reported as treatment related and unrelated (21)).
- Mortality, evaluated with number of deaths.

Secondary outcome

- Study withdrawal for any reason
- Study withdrawal due to adverse events

Data extraction (selection and coding)

Data will be extracted from each trial using a pre-specified form. A reviewer will extract data from the included studies which will subsequently be verified by a second reviewer. Disagreements will be clarified by consensus and, when needed, a third reviewer will act as an adjudicator.

From each selected trial, we will collect:

- general study information (specified previously (1))
- type of intervention(s) (incl. dose, frequency of administrations, type of administration, and subsequently divided into three dose categories according to the product labelling: [high, low, or recommended respectively])
- type of comparator(s)

- study duration (i.e. longest controlled period)
- number of randomised individuals for each treatment group
- number of subjects experiencing at least one SAE for each treatment group (when only the number of events instead of the number of subjects experiencing an event is reported, an assumption of one event per subject will be made)
- number of deaths for each treatment group
- number of treatment related and unrelated deaths for each treatment group
- number of subjects who withdrew from the study (dropouts) for each treatment group
- number of subjects who withdrew due to adverse events for each treatment group
- total person years for each treatment group (if not reported it will be estimated by assuming a linear dropout rate between time points at which subject status is known)
- Allowed background medication not part of allocation (i.e. NSAIDs, glucocorticoids, csDMARDs)
- Inclusion of patients with comorbid conditions (yes/no)
- Early escape option (e.g. rescue treatment) (yes/no)

Risk of bias and quality assessment

This project focuses on safety rather than efficacy but we will use the approach recommended by the Cochrane Collaboration as a base case (22). The Cochrane risk of bias tool consists of five items for which there is empirical evidence for their biasing influence on the estimates of an intervention's effectiveness in randomised trials (sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting) and a flexible item called "other sources of bias"; i.e., with regard to safety reporting we decided to extract whether the trial had any elements of an adaptive trial design after the primary outcome assessment, which was coded as "yes" if an early rescue option was applied in any of the groups.

Evidence across studies for each b/tsDMARD for each outcome will be assessed using criteria suggested by the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) Working Group (23).

Strategy for data synthesis

Our meta-analysis will be performed using Review Manager version 5.3 (Cochrane IMS) and SAS version 9.3. We will perform both standard pairwise meta-analysis and network meta-analysis.

Pairwise meta-analysis will be conducted (using the subgroup feature for each of the 10 evaluated drugs applied in recommended dose [or equivalent]) comparing a b/tsDMARD vs. no-b/tsDMARD (± csDMARD[s] in both groups). In cases where a study include more than one treatment group that could be categorised as "recommended dose" these particular groups will be combined to create a single group (e.g. adalimumab 40mg/2 weeks and adalimumab 20mg/week) insets of splitting the control group into 2 equal groups.

Two types of pairwise meta-analysis approaches will be performed. The first approach will be based on number of subjects experiencing an event (numerator) and the number of subjects randomised (denominator) and the result will be expressed as odds ratios. The second approach will account for follow-up time and be based on the number of subjects experiencing an event (numerator) and the (estimated) total person years (denominator) and the result will be expressed as rate ratios (24); in which case the (count) data are modelled assumed to follow a Poisson distribution. Because we suspect zero-event data in some groups and imbalances in patient numbers and person years between study arms, we will use a continuity correction when there are no events observed in 1 study arm of a trial. This correction will be the inversely proportional to the relative size of the opposite of the study arm (e.g. the continuity correction for the treatment arm is 1/[R+1], where R is the ratio of control group to intervention group sizes. Similarly, the continuity correction for the control arm is R/[R+1] (25)).

Although the studies are likely not representing a "fixed sample" of studies, we will apply the inverse-variance summary risk difference and rate difference where the individual trial estimates are weighted according to the reciprocal of their estimated variance. All pairwise meta-analysis estimates will be presented as forest plots with both individual studies and the combined estimates presented with 95% confidence intervals (95%CI). In addition to reviewing forest plots, we shall statistically analyse heterogeneity of the data using the Cochran's Q- test (26); the I^2 index will be applied to ease interpretation and quantify the amount of inconsistency (27).

Network meta-analysis will be performed to mutually compare each of the 10 evaluated drugs. Unlike a contrast-based (standard) meta-analysis approach, a network meta-analysis enables us to

combine trials including both direct and indirect comparisons; i.e., referred to as an arm-based approach (28). For the network meta-analysis, we will perform mixed-effects logistic and Poisson regression using an arm-based, random effects model within an *empirical Bayes* framework (19); the generalized linear mixed model (GLMM) incorporates a vector of random effects and a design matrix for the random effects (29). Allowance is made for differences in heterogeneity of effects between different drugs by specifying that the linear predictor varies at the level of study and the drug across. In the network meta-analyses, we shall measure heterogeneity (i.e., between study variance) for the analysis using T^2 (an estimate for Tau-squared), which examines heterogeneity because of *Study* and *Study×Drug* interaction (smaller values indicate a better model *per se;* less variance between the studies). These network meta-analyses will scrutinize models across treatment classes and dose levels, and models involving constraints on the impact of dose level (recommended, low, high), as well as the impact of concomitant use of csDMARD(s). These models provide a flexible approach to estimating sparse, adverse outcomes associated with different interventions as recently described by Warren *et al* (30). The data will be modelled using PROC GLIMMIX provided in SAS version 9.3. As in the pairwise meta-analysis, a nominal significance level of 5% will be applied in the subsequent interpretation of statistical significance, including presenting all results with 95% CIs.

Similar to the pairwise meta-analysis two types of network meta-analysis approaches will be performed. The first approach will be based on number of subjects experiencing an event (numerator) and the number of subjects randomised (denominator) – expressed as odds ratio's. The second approach will adjust for follow-up time and be based on the number of subjects experiencing an event (numerator) and the total person years (denominator) – expressed as rate ratio's. Each outcome will be fitted into a mixed-effects logistic and Poisson regression with study as a random effect and treatment as a fixed effect.

Analysis of subgroups or subsets

Several sensitivity analyses will be performed as recommended for meta-analysis of rare events (31). For the pairwise meta-analysis we will perform a risk ratio, and a risk difference - inverse variance meta-analysis for outcomes evaluated as events per subject randomised. Both

analyses will be completed handling zero-cell with different corrections: (i) the reciprocal of the opposite group arm size (25)), (ii) adding 0.5 to each cell (default in RevMan), (iii) excluding trials with zero event-cells. Further, we will apply the Mantel-Haenszel method for risk difference, risk ratio, and odds ratio and the Peto odds ratio method (31). For outcomes evaluated as events per person years we will complete a rate difference inverse variance meta-analysis (24) with handling zero-cell with different corrections: (i) the reciprocal of the opposite group arm size, (ii) adding 0.5 to each cell, (iii) excluding trials with zero event-cells. For the network meta-analysis we will explore different models suggested by Warren *et al* (30). Subgroup analyses will be performed to check whether follow-up (up to 3, 6, 12, 24, and 36 months) will change our findings and whether a dose-harm relationship exist (recommended, low, high).

Dissemination

Although there is a possibility that the quality of the data, the relatively low number of trials for each drug, and the low incidence of SAE and in particular deaths will allow a meaningful network meta-analysis we believe this study will be highly relevant as the effect of any anti-rheumatic therapy on serious adverse effects is particularly important. The consequences from revelations of harm associated with several widely prescribed drugs, has led to widespread recognition that improvement is needed ensuring drug safety (32).

The results will be disseminated as article(s) in peer-reviewed scientific journal(s), and will be communicated via scientific meetings as well as presented for public outreach to patients and the public via suitable sources. Papers will be drafted by the primary investigator and revised by the collaborators, who will be authors when they provide substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; are part of drafting the work or revising it critically for important intellectual content; and will be part of the final approval of the version to be published. Finally all authors need to be in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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