

**DEFINING THE OPTIMAL BIOLOGICAL MONOTHERAPY IN
RHEUMATOID ARTHRITIS:
NETWORK META-ANALYSIS OF RANDOMIZED TRIALS**

[PROTOCOL]

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PROTOCOL SYNOPSIS

Background: Pharmacological therapy in Rheumatoid Arthritis (RA) patients includes both conventional disease-modifying antirheumatic drugs (DMARDs) and biological agents. Currently the biologic agents include nine that are all approved for RA: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, abatacept, rituximab, and tocilizumab. Methotrexate (MTX) is considered the anchor drug in RA, both as monotherapy, as well as its ability to increase the efficacy of biologic agents when used in combination. However, it is estimated that between 10 and 30% of RA patients are MTX-intolerant and discontinuation is common in clinical practice. Thus, it is important to evaluate a switch strategy to biological monotherapy.

Objective: To review the evidence for efficacy and safety of biologic monotherapy in RA. The overall goal is to define the optimal biological monotherapy in RA patients without concomitant MTX therapy.

Design: Systematic review and Network meta-analysis of randomized controlled trials (RCTs). Emphasis will be on each of the following strata: 'Clinically active MTX-naïve (or equivalent) RA patients' vs. 'Active RA despite MTX therapy (Bio-Naïve)' vs. 'Active RA previously received one or more biological therapies'.

Data sources: Bibliographic databases, conference proceedings, reference lists of relevant articles, and reports citing relevant articles. Manufacturers of biologics will be contacted if additional data are needed. All RCTs in a population of RA patients, including a biologic agent in monotherapy are considered eligible. Two investigators will assess for eligibility. The co-primary outcome is the number of patients achieving an ACR50 response, and the number discontinuing therapy due to adverse events after 6 months, respectively. Secondary outcomes include ACR20, ACR70, number of withdrawals, and Serious Adverse Events. Two investigators will extract data.

Methods: The network meta-analysis will be based on mixed-effects logistic regression combining statistical inference from both direct and indirect comparisons of the treatment effects between biologics.

Results: Results will be submitted as an abstract to the EULAR 2013 conference; final full article manuscript will be submitted to a peer reviewed journal December 2012.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease that affects the synovial joints. RA is characterized by pain, swelling, and destruction of joints, with resultant disability (1). The inflammation in RA patients should be suppressed as early as possible (1;2); only disease-modifying antirheumatic drugs (DMARDs) can interfere with the disease process (3). Pharmacological therapy in RA patients includes both conventional DMARDs and new biological DMARDs (4;5). DMARDs are effective for both symptoms and signs of RA, although biological agents apparently offer greater suppression of progression of structural damage (2;6). Conventional DMARDs includes hydroxychloroquine, leflunomide, methotrexate (MTX), and sulfasalazine; these DMARDs are also used in various combinations (5). DMARD combination therapy includes 2 drugs, most of which are MTX based with only a few exceptions (5); these are given either with or without concomitant glucocorticoid therapy (4).

The term biological describes treatments developed and produced in live cell systems; these drugs are also referred to as biological therapies or cytokine modulators (7). These biologics are targeted therapies that dramatically inhibit the progression of joint damage in RA, and improve the disease status in RA patients (8;9). Currently the biologic agents include the following nine that are all approved for RA and other conditions: five tumor necrosis factor inhibitors (TNFi) - adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; available is also anakinra, abatacept, rituximab, and tocilizumab with another mode of action (10).

Before the patients initiate therapy with a biologic agent they will frequently be prescribed methotrexate (MTX). MTX is among the most effective DMARDs in RA with less toxicity and better tolerability. Unfortunately, MTX alone may not fully control disease activity. Patients unresponsive to MTX or other DMARDs may receive biologic agents as monotherapy, or in combination with MTX. Anti-TNF biologics (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) differ in

composition, precise mechanism of action, pharmacokinetics and biopharmaceutical properties, but are also frequently considered on the basis of their areas of commonality. Non-TNF biologics (abatacept, anakinra, rituximab, and tocilizumab): abatacept is an agent which modulates T-cell. Rituximab is a chimeric anti-CD20 monoclonal antibody, which eliminates CD20 positive B-cells. One IL-1-blocking agent, anakinra (IL-1 receptor antagonist), has been approved for use in RA. Tocilizumab is a humanised anti-IL-6 receptor monoclonal antibody.

MTX should be part of the first treatment strategy in patients with active RA. According to the recommendations from the 'European League Against Rheumatism' (EULAR), when MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the treatment strategy: leflunomide, sulfasalazine or injectable gold (4). MTX is considered the anchor drug in RA, both on the basis of its efficacy and safety as monotherapy, as well as its ability to increase the efficacy of biologic agents when used in combination (11). The American College of Rheumatology (ACR) recommends the use of an anti-TNF biologic with or without MTX in patients who have high disease activity with poor prognostic features; infliximab is the only exception and the recommendation is to use it in combination with methotrexate, but not as monotherapy. It is estimated that between 10 and 30% of RA patients are MTX-intolerant and discontinuation is common in clinical practice (12). Adverse effects from long-term MTX use are ulcerative stomatitis, leukopenia, nausea, increased liver transaminases and abdominal distress. For those patients who require treatment with a biologic agent and cannot tolerate MTX, combination therapy with other DMARDs or biological monotherapy is necessary. Moreover, the need for biologic monotherapy options may be important for RA patients who are also receiving treatment for other conditions (13).

There are many reasons for stopping MTX or initiating biological agents as a monotherapy. In daily practice, frequent methotrexate-induced gastrointestinal disorders (e.g., nausea)

have been reported as leading to poor patient compliance. The use of MTX may lead to other safety issues such as hematological and hepatic adverse events (14). Such limitations explain why it is important to evaluate a switch strategy to biological monotherapy in addition to traditional add-on strategies (i.e., the addition of a biological agent to MTX) (15;16).

Objectives

To review the evidence for efficacy and safety of biologic monotherapy in RA. The overall goal is to define the optimal biological monotherapy in RA patients who cannot tolerate MTX or where use of MTX is inappropriate, combining both direct and indirect evidence in a network meta-analysis of randomized trials.

METHODS

Protocol and registration

Study selection, assessment of eligibility criteria, data extraction, and statistical analysis will be based on this predefined protocol according to the Cochrane Collaboration guidelines (<http://www.cochrane-handbook.org/>); the results will be reported according to the recommendations given in the PRISMA statement (17).

Eligibility criteria

A systematic review will be performed to identify randomized controlled trials (RCTs), which investigated the efficacy of a biologic agent administered as monotherapy in RA. Eligible patients had confirmed RA presumably according to the 1987 ACR-criteria. The biologic agents of interest for this particular network meta-analysis include nine that are all approved for RA: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, abatacept, rituximab, and tocilizumab.

Information sources:

A thorough and comprehensive literature search for RCTs, all looking at the biologic agents for RA, will be carried out with last search 1st September 2012. The following bibliographic databases will apply: MEDLINE via PubMed from 1950, EMBASE via OVID from 1980, CINAHL via EBSCO from 1981, Chemical Abstracts via Scifinder from 1907, and Web of Science from 1900, as well as The Cochrane Central Register of Controlled Trials, to identify all trials relating Biologics to RA. Further searches will be undertaken for the American College of Rheumatology (ACR) and the 'European League Against Rheumatism' (EULAR) conferences in 2011 and 2012.

As the area of evidence-synthesis in "Biologics for RA" is not a novel research area, we will also manually apply a search strategy for cited articles from previous meta-analyses available from PubMed:

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rheumatoid[title] AND (meta analysis[pt] OR (meta analyse[ti] OR meta analysed[ti] OR meta analyses[ti] OR meta analysesresearch[ti] OR meta analysing[ti] OR meta analysis[ti] OR meta analysisof[ti] OR meta analyst[ti] OR meta analysticians[ti] OR meta analysts[ti]) OR (metaanalyses[ti] OR metaanalysis[ti]) OR (meta regressed[tiab] OR meta regression[tiab] OR meta regression'by[tiab] OR meta regressional[tiab] OR meta regressions[tiab] OR meta regressive[tiab]) OR (metaregress[tiab] OR metaregression[tiab] OR metaregressions[tiab] OR metaregressive[tiab]) OR (multiple[All Fields] AND compar[All Fields]) OR (indirect[All Fields] AND compar[All Fields])) AND (( "adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]) OR ("certolizumab pegol"[Supplementary Concept] OR "certolizumab pegol"[All Fields] OR "certolizumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields] OR "etanercept"[Supplementary Concept]) OR ("golimumab"[Supplementary Concept] OR "golimumab"[All Fields]) OR ("infliximab"[Supplementary Concept] OR "infliximab"[All Fields]) OR ("interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "anakinra"[All Fields]) OR ("abatacept"[Supplementary Concept] OR "abatacept"[All Fields]) OR ("rituximab"[Supplementary Concept] OR "rituximab"[All Fields]) OR ("tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields]))
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This search will also be supported by the Medline search strategy for systematic reviews as proposed by Montori et al; empirical

search terms for high sensitivity (.98%) in retrieval of systematic reviews (18).

Study selection:

We include randomized, controlled trials of patients with RA that include any of the nine biologics administered as monotherapy. Two reviewers (RC, ST) will independently evaluate reports for eligibility. Disagreements will be resolved by discussion (LEK & HB). No language restrictions apply.

Data collection process

The data extraction will be performed by one researcher (RC) and reviewed by another (ST); meaning, effectively, that the second reviewer will trace back every value/number/comment to the original full text report and validate the extracted data. A standard data-extraction form is developed for data collection. The following information is systematically extracted as characteristics of the studies for each of the k randomized trials, and handled in a customized Microsoft Excel spreadsheet: Demographic baseline variables, study duration, dosage, attrition, and report of the size of the original intention-to-treat population.

Participants and setting. The following study level characteristics will be collected from all the eligible trials: Rheumatoid Factor status (%), Number of females (%), Mean age (years), Median (or mean) number of years since RA diagnosis, Number of patients on glucocorticoids (%), the mean 'Tender-' and 'Swollen-' Joint Count (TJC and SJC, respectively), the mean patient global assessment (mm VAS).

Types of outcome measures. The core-outcome data in each study consist of the sample size of the groups, the number of patients in each group who 'had an event'. *A priori* it was decided to use the outcome assessment after on average 6 months varying according to the original protocols (i.e., 24-26 weeks) in each trial. Two major outcomes will be considered our co-primary outcomes: Benefit

(defined as a 50% improvement in the American College of Rheumatology symptomatic criteria [ACR50] (19)) and Harm (determined by the number of withdrawals because of adverse events (20)). ACR50 is a validated clinically meaningful binary measure of benefit (21). It is defined as a 50% improvement in swollen and tender joint counts plus a 50% improvement in 3 out of 5 clinically important criteria. For safety, we chose to include withdrawals that occurred because of adverse events, which is a measure of patients' tolerance of adverse events and is reported consistently (21).

The secondary benefit outcomes will include the number of patients achieving an ACR20, and ACR70 response, respectively; whereas, the secondary outcomes for harm will be the number of patients who withdraw from the study, and the number of patients who are having a serious adverse event (SAE). We anticipate these, together with the co-primary outcomes, will enable a simplistic version of the 'Outcome Measures in Rheumatology [OMERACT] 3x3 table' that comprises three ranks for both benefit and harm outcomes (22).

Risk of bias in individual studies:

Empirical studies show that inadequate quality of trials may distort the results from meta-analyses. Therefore, influence of quality of included studies should be included in meta-analyses at least for the purpose of sensitivity analysis. Two of the reviewers (RC & ST) will independently assess (i) randomization followed by concealment of treatment allocation, (ii) blinding, and (iii) adequacy of statistical analyses (i.e., proper intention-to-treat [ITT] analysis) (23):

Randomization and concealment of allocation is considered adequate if the investigators responsible for patient selection were unable - prior to allocation - to suspect which treatment was next.

Blinding is considered adequate if participants and key study personnel ensured complete lack of knowledge of treatment

allocation, and that it was unlikely that the blinding had been broken.

Statistical analyses are considered adequate if all randomized patients were analyzed in the group to which they were randomly allocated, regardless of the treatment received (ITT principle). Modified ITT population/analysis will most likely be categorized as unclear.

The assessment of each entry involved answering a question, with answer 'A' indicating low risk of bias (adequate reporting), 'B' indicating unclear (either lack of information or uncertainty concerning the potential for bias), whereas 'C' refers to an inadequate handling of the item (i.e., high risk of bias per se) (23). Disagreements will be resolved by consensus (incl. LEK & HB).

Synthesis of results

When 2 drugs are compared with a common standard, the difference in effect between these 2 drugs with respect to the common standard forms the basis of indirect comparisons. In rheumatology, most biologics will be used in conjunction with other baseline DMARDs and compared with MTX and the same (i.e., equally distributed concomitant) baseline therapy. Indirect treatment comparisons in meta-analysis can be analyzed by various methods according to the different networks applied, including the star, ladder, closed and partially closed-loop designs (24). We use the star design and include at least 1 mono-biologic group from each available trial.

We perform mixed-effects logistic regression using an arm-based, random-effects model within an empirical Bayes framework. The generalized linear mixed model (GLMM) incorporates a vector of random effects and a design matrix for the random effects (25). 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 study.

The primary model will also include the following covariates (attempting to) adjust for important confounders: average age, percentage of females, and the median (or mean) disease duration.

We will present approximated inconsistency indices (I^2) for each of the drugs compared with DMARD (ranging from 0% to 100%, higher values indicate more heterogeneity). Formally, however, we will evaluate heterogeneity for the direct and indirect network of comparisons using estimated covariance parameters (Tau-squared estimated from GLMM in SAS v. 9.2), which examines heterogeneity because of 'Study' and 'Study×Drug' interaction (smaller values indicate a better model fit *per se*).

Stratified analyses

The overall goal of this evidence synthesis project is to determine which of the biologic therapies that are most likely to result in a significant disease reduction (>50%) from the patients' and physicians' perspective (ACR50), without causing harm that will make the patient want to discontinue therapy. We pre-specify that the following stratified analyses would add value to clinical decision making, thus, these will also be added to the statistical model:

Primary:

- *MTX-naïve (or equivalent) RA patients vs. Active RA despite MTX therapy (Bio-Naïve) vs. Active RA previously received one or more biological therapies*

Secondary:

- *MTX-naïve & Active RA despite MTX therapy vs. Previous use of Biologic*
- *Anti-TNF α Biologic vs. Non-TNF α Biologic*

Risk of bias across studies:

In order to empirically assess the Risk of Bias in our estimates, we will perform analyses stratified by the different Risk of Bias trial characteristics: concealment of allocation, blinding (i.e., double-dummy technique), adequacy of analyses in accordance with

the intention-to-treat principal (23).

RESULTS

Timeline (anticipated)

- March–May (2012): Preparing the Synopsis
- May–August 15 (2012): Approval of the final protocol (registration in PROSPERO – International prospective register of systematic reviews)
- August 15–September 31 (2012): Literature search & data extraction
- December 2012: Manuscript 1st Version.

PERSPECTIVES

In RA patients with active disease, who are intolerant to MTX and need biological monotherapy, it is important that we provide the RA patients with the most optimal treatment strategy; optimal treatment strategy includes explicit considerations on benefit and harm in both relative and absolute terms. It is prudent that this informed decision making is based on empirical evidence rather than a “clinical gut feeling”, even if this subgroup of RA patients only represent a “minority” (i.e., 10–30% probably do not tolerate MTX).

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