

ADDED-VALUE OF COMBINING METHOTREXATE WITH A BIOLOGICAL AGENT COMPARED TO BIOLOGICAL MONOTHERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS:

Protocol for a systematic review and meta-analysis of randomised trials

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CONFLICTS OF INTEREST

TSJ: has received research grants paid to institute: AbbVie and Roche

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ABSTRACT

Background

Methotrexate (MTX) is considered the anchor drug in rheumatoid arthritis (RA) treatment, 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. Both the 'American College of Rheumatology' (ACR) and the 'European League Against Rheumatism' (EULAR) recommends the use of biologic agents with concomitant use of MTX in patients with RA. However, analyses from health care claims suggest that when MTX is prescribed in conjunction with a biologic disease-modifying antirheumatic drug (bDMARD), more than half of the patients do not collect the MTX prescription. Despite the clinical use of MTX in combination with a bDMARD for decades, the actual benefit-harm associated with combining MTX to biologics has not been evaluated extensively.

Objectives

To review the evidence for benefit and harm associated with combining MTX to a biologic agent in RA patients. The overarching goal is to define the value of combining MTX to a bDMARD in patients with RA.

Methods

A systematic literature search of The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE will be conducted. 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, The 'Food and Drug Administration' (FDA) Approved Drug Products reviews, The 'European Medicines Agency' (EMA) and pharmaceutical company's online databases as well as electronic abstract databases of the annual scientific meetings of both the 'American College of Rheumatology' (ACR) and the 'European League Against Rheumatism' (EULAR) to identify unpublished data. We will include randomized controlled trials (RCTs) of patients with RA that compare a bDMARD with and without concomitant administration of MTX.

Dissemination

Rational use of pharmacotherapy in RA is prudent for the patient's quality of life, disablement, joint destruction, morbidity in general, and death. Although guidelines from both ACR and EULAR recommend adding MTX to a biologic agent on the basis of its ability to increase the efficacy of biologic agents when used in combination, analyses from health data claims that more than 50% do not collect their MTX prescription. If combining MTX with a biologic increase the value of treatment, rheumatologists may play an important role in the patient's adherence behaviour. Decision and policy makers need a transparent evidence base to substantiate the judgment behind any rational clinical rheumatology practice, and this systematic review and meta-analysis will contribute to this.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most frequently occurring autoimmune rheumatic diseases, affecting an estimated 1% of the global population (1;2). The chronic inflammation that underpins this disease leads to synovial inflammation and effusion, ultimately followed by joint destruction and permanent disability. RA patients should be treated as early as possible with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) to improve the disease course (3-5).

The primary goal of therapy in RA patients is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation (6). Among the csDMARDs, methotrexate (MTX) is considered the anchor drug in RA treatment, 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 (7-9).

The 'American College of Rheumatology' (ACR) and the 'European League Against Rheumatism' (EULAR) recommends the use of biologic agents with concomitant use of MTX in patients who have high disease activity with poor prognostic features (10;11). Currently the biologic agents include the following nine that are all approved for RA and other conditions: five tumour necrosis factor inhibitors (TNFi) – adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; available is also anakinra, abatacept, rituximab, and tocilizumab with another mode of action (12).

Registries of routine clinical practice treatment indicate that approximately one third of RA patients are being treated with biological monotherapy (13-18). Although MTX is among the best-tolerated disease-modifying antirheumatic drugs (19-22) analyses from health care claims suggest that when MTX is prescribed in conjunction with a bDMARD, more than half of the patients do not collect the MTX prescription (23).

Despite the clinical use of the combination of biologic DMARDs (bDMARDs) and MTX for more than a decade, the actual benefit-harm associated with MTX (including different doses) compared to biologics alone has not been evaluated extensively.

Objectives and goals

The overarching goal of this evidence synthesis project will be to assess the efficacy and safety of combining MTX to a biological agent compared to the biologic agent alone for patients with RA. The objective is to assess and evaluate the benefit and harm associated with combining MTX to a biologic agent (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab) in RA patients with active disease. Secondly we want to explore whether the effect of combining MTX to a biological agent vary across different “RA populations”, as well as determining whether the success of some biologics are more dependent on MTX than others.

METHODS

Methods of the analysis and inclusion criteria is specified and documented in this protocol (PROSPERO: CRD42014014633). Both protocol and analyses are prepared according to the ‘Methodological Expectations for Cochrane Intervention Reviews’ (MECIR) programme. Our paper conforms to the recommendations given in the PRISMA guidelines for reporting systematic reviews and meta-analysis (24).

Eligibility criteria

All RA randomised controlled trials (RCTs) evaluating the effect of combination treatment with any bDMARD (25) and MTX versus the bDMARD alone will be considered eligible for inclusion. For both bDMARDs and MTX no restrictions on dose, treatment duration, administration procedures, and co-medication will be imposed. The bDMARDs of interest for this particular meta-analysis include the nine that are all approved for RA: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab.

Eligible patients have confirmed RA, presumably based on well-established clinical definitions from the American College of Rheumatology (ACR) criteria (26) or equivalent. Two reviewers (TSJ, ST) will independently evaluate reports for eligibility.

Information sources

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 (27). 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 following approach: 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 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 following search: (TITLE:(rheumatoid) AND TITLE:(cimzia OR simponi OR rituxan OR orenicia 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.

Data collection process

Details of participants and setting are collected primarily for presentation in the table of characteristics of included studies. We extract those that could affect presence or magnitude of an intervention effect and those that could help users assess applicability - incl. design, selection

criteria, characteristics of the study population, interventions (i.e. dose, administration form, and frequency of administration for both MTX and biologics), MTX titration regime, folic acid regime, outcome measures, length of follow-up and results. Two reviewers (TSJ, ST) will independently extract data. If necessary, we shall write to the corresponding authors to provide additional relevant information. We shall resolve by consensus any disagreements about extracted data and consult a third reviewer if required. In brief we shall extract details of:

Participants and setting: Number of females (no. %), age (years), disease duration (years), IgM rheumatoid factor status (no. %), MTX history (MTX naïve/MTX failure/ MTX mixed), corticosteroid allowed during trial (yes/no/unclear), intra-articular GC as rescue treatment (yes/no/unclear), other csDMARDs allowed as background treatment during trial (stable continued during trial/ discontinued before randomisation/not using at randomisation/unclear), and inclusion of patients with co-morbidities (e.g. diabetes, thyroxin disease, fibromyalgia, gout, osteoarthritis, cancer) (yes/no/unclear).

Types of outcome measures: A priori it is decided to use the outcome assessment after 6 months varying according to the original protocols in each trial. The major outcomes for benefit and harm will follow the recommendations from the Cochrane Musculoskeletal Group (CMSG) (28). A priori the “co-primary outcome” was defined as ACR50 for *benefit* (defined as a 50% improvement in the American College of Rheumatology symptomatic criteria [ACR50]) (29), and the number of withdrawals because of adverse events will be applied as a proxy for *harm* (30). ACR50 is a validated clinically meaningful binary measure of benefit (31). For safety, we chose to include withdrawals that occurred because of adverse events, which is a measure of patients’ tolerance of adverse events and should be reported consistently (31). Further we will extract the following major outcomes: ACR20; DAS28 remission (or low disease activity [LDA]); health assessment questionnaire (HAQ) for function; radiograph progression; serious adverse events (SAE); number of serious adverse events per patient year (SAE/PY); serious infections (SAE-Inf), withdrawals due to any causes, gastrointestinal adverse events, and adverse events due to elevated liver enzymes.

Risk of bias in individual studies

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. Quality assessment will be performed using the risk of bias tool from the Cochrane Collaboration. Two reviewers (TSJ, ST) will independently assess the following domains Selection bias: (i) randomisation technique followed by (ii) concealment of treatment allocation; Performance bias: (iii) blinding of participants and personnel; Detection bias (iv) blinding of outcome assessment; Attrition bias (v) incomplete outcome data and adequacy of statistical analyses (i.e., proper intention-to-treat [ITT] analysis). After considering each item in all the trials, each of the key bias domains will be categorised as either Adequate (indicating low risk of bias), Unclear (either lack of information or uncertainty concerning the potential for bias), or Inadequate (i.e., high risk of bias per se) (32).

Data synthesis

In the first stage when we report data from each of the included studies some are dichotomous (33), whereas others are continuous (34). For dichotomous (binary) outcomes the results of each study can be presented in a 2x2 table giving the numbers of participants who do or do not experience the event in each of the two groups. If the outcome is a continuous measure, the number of participants in each of the two groups, their mean response and the standard deviation of their responses are required to perform meta-analysis. We will express dichotomous outcomes as risk ratios (RR) and calculate the corresponding 95% CIs for each study. For continuous variables, we will compare net changes and calculate a standardised mean difference (SMD) with 95%CI for each study (applicable when the studies assess the same outcome but measure in different ways) (35).

In the second stage, a summary (pooled) intervention effect estimate will be calculated as a weighted average of the intervention effects estimated in the individual studies. As we anticipate heterogeneity across studies (i.e., differences in study effects that cannot readily be explained), we will incorporate it into a random-effects model (36). All data will be entered into

Review Manager 5, and additional stratified and meta-regression analyses will be performed using SAS software (PROC MIXED version 9.3; SAS Institute Inc., Cary, NC, USA). In addition to reviewing forest plots, heterogeneity of the data will be tested using the chi-square test (37) and evaluated via the I^2 index for inconsistency, which can be interpreted as the percentage of total variation across several studies due to heterogeneity (38). An I^2 value greater than 50% will indicate substantial inconsistency. In the case of substantial heterogeneity, the data will be explored further, including the protocolised stratified analyses, in an attempt to explain (i.e., reduce) the heterogeneity.

Stratified analysis

The overall goal of this evidence synthesis project is to determine the efficacy (ACR 50) and safety (withdrawal from therapy due to adverse events) of combining MTX to a bDMARD compared with a bDMARD administered without concomitant MTX, without causing harm that will make the patient want to discontinue therapy.

We will perform stratified analyses, in order to explore the quantitative impact of patient characteristics and duration of study. Following stratified analyses that will add value to clinical decision-making, thus, these will be added to subsequent statistical models, we want to compare whether the effect of adding MTX varies with:

- The choice of bDMARD therapy
- bDMARD modes of action (TNF blocking agents/ interleukin-6 blocking agents/ interleukin-1 blocking agents/ B cell specific agents)
- MTX history (MTX naïve/MTX failure/MTX mixed)
- MTX at randomisation per arm (stable continued during trial/ discontinued before randomisation/ not using at randomisation/unclear)
- MTX dose
- MTX administration form
- Other csDMARDs (stable continued during trial/ discontinued before randomisation/ not using at randomisation/unclear)

To assess the risk of bias in our estimates analyses stratified by the different risk of bias trial characteristics will be performed.

DISSEMINATION

Rational use of pharmacotherapy in RA is prudent for the patient's quality of life, disablement, joint destruction, morbidity in general, and death. Over the last two decades, MRI has emerged as an important clinical tool to assist in the diagnosis and management of rheumatic disease. MRI as a marker of outcome in clinical trials is being paralleled by its increasing role in the clinic.

Given the success of biologic therapies in combination with MTX, it is important to assess and evaluate the benefit and harm associated with the value of adding MTX to bDMARDs. Although guidelines from both ACR and EULAR recommend combining MTX to a biologic agent both on the basis of its efficacy and safety as monotherapy, and its ability to increase the efficacy of biologic agents when used in combination, analyses from health data claims that more than 50% do not collect their MTX prescription. If combining MTX to a biologic increases the value of treatment, and ensure maintenance of therapy in the long term, rheumatologists may play an important role in the patient's adherence behaviour.

Because of the high prices of biologics, their cost-effectiveness is also a matter of debate. This may be a reason why different official treatment recommendations are not completely concordant. New studies have found combination of csDMARDs non-inferior to the coveted biologics with MTX along with greatest economic advantage to their credit. Future study designers should not seek superiority of the new drug compared with placebo, but should design studies with sufficient power to demonstrate superiority with a combination of csDMARDs. Decision and policy makers need a transparent evidence base to substantiate the judgment behind any rational clinical rheumatology practice, and this systematic review and meta-analysis will contribute to this.

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 (incl. the Danish Rheumatism Association). 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.

TIMELINE (anticipated)

<i>Draft protocol</i>	<i>22th of September – 15th of October</i>
<i>Protocol approval and publication</i>	<i>15th of October – 1st of November</i>
<i>Literature search and data extraction</i>	<i>1st of November – 30th of November</i>
<i>Data processing at the Parker Institute</i>	<i>1st of December – 31st of December</i>
<i>Draft manuscript</i>	<i>December 2014 / January 2015</i>
<i>Abstract submission EULAR 2015</i>	<i>31st of January 2015</i>

Reference List

- (1) Spector TD. Rheumatoid arthritis. *Rheum Dis Clin North Am* 1990 Aug;16(3):513-37.
- (2) Wolfe F, Rasker JJ, Boers M, Wells GA, Michaud K. Minimal disease activity, remission, and the long-term outcomes of rheumatoid arthritis. *Arthritis Rheum* 2007 Aug 15;57(6):935-42.
- (3) Emery P, Kvien TK. Treating rheumatoid arthritis. *BMJ* 2007 Jul 14;335(7610):56-7.
- (4) Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 2004 Jul;43(7):906-14.
- (5) Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewe R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2014 Jan;73(1):3-5.
- (6) Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010 Apr;69(4):631-7.
- (7) Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. *Stat Med* 2007 Mar 15;26(6):1237-54.
- (8) Lie E, van der Heijde D, Uhlig T, Mikkelsen K, Kalstad S, Kaufmann C, et al. Treatment strategies in patients with rheumatoid arthritis for whom methotrexate monotherapy has failed: data from the NOR-DMARD register. *Ann Rheum Dis* 2011 Dec;70(12):2103-10.
- (9) Pincus T, Gibson KA, Castrejon I. Update on methotrexate as the anchor drug for rheumatoid arthritis. *Bull Hosp Jt Dis (2013)* 2013;71 Suppl 1:S9-19.
- (10) Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2013 Oct 25.
- (11) Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012 May;64(5):625-39.
- (12) Furst DE, Keystone EC, So AK, Braun J, Breedveld FC, Burmester GR, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis* 2013 Apr;72 Suppl 2:ii2-34.
- (13) Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients

- with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. *Arthritis Rheum* 2008 Feb 15;59(2):234-40.
- (14) Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011 Apr;70(4):583-9.
 - (15) Listing J, Strangfeld A, Rau R, Kekow J, Gromnica-Ihle E, Klopsch T, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low--results from RABBIT, the German biologics register. *Arthritis Res Ther* 2006;8(3):R66.
 - (16) Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann Rheum Dis* 2007 Oct;66(10):1339-44.
 - (17) Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology (Oxford)* 2011 Jan;50(1):222-9.
 - (18) Lee SJ, Chang H, Yazici Y, Greenberg JD, Kremer JM, Kavanaugh A. Utilization trends of tumor necrosis factor inhibitors among patients with rheumatoid arthritis in a United States observational cohort study. *J Rheumatol* 2009 Aug;36(8):1611-7.
 - (19) Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. *Arthritis Rheum* 1990 Oct;33(10):1449-61.
 - (20) Felson DT, Anderson JJ, Meenan RF. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis. A metaanalysis of published clinical trials. *Arthritis Rheum* 1992 Oct;35(10):1117-25.
 - (21) Fries JF, Williams CA, Ramey DR, Bloch DA. The relative toxicity of alternative therapies for rheumatoid arthritis: implications for the therapeutic progression. *Semin Arthritis Rheum* 1993 Oct;23(2 Suppl 1):68-73.
 - (22) Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. *J Rheumatol* 1992 Dec;19(12):1885-94.
 - (23) Emery P, Sebba A, Huizinga TW. Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis. *Ann Rheum Dis* 2013 Aug 5.
 - (24) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009 Oct;62(10):e1-34.
 - (25) Tugwell P, Singh JA, Wells GA. Biologicals for rheumatoid arthritis. *BMJ* 2011;343:d4027.

- (26) Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988 Mar;31(3):315-24.
- (27) Dossing A, Tarp S, Furst DE, Gluud C, Beyene J, Hansen BB, et al. Interpreting trial results following use of different intention-to-treat approaches for preventing attrition bias: a meta-epidemiological study protocol. *BMJ Open* 2014;4(9):e005297.
- (28) Ghogomu EA, Maxwell LJ, Buchbinder R, Rader T, Pardo PJ, Johnston RV, et al. Updated method guidelines for cochrane musculoskeletal group systematic reviews and metaanalyses. *J Rheumatol* 2014 Feb;41(2):194-205.
- (29) Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. *Ann Rheum Dis* 2006 Dec;65(12):1602-7.
- (30) Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004 Nov 16;141(10):781-8.
- (31) Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ* 2009 Nov 24;181(11):787-96.
- (32) Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- (33) Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *J Clin Epidemiol* 2011 Dec;64(12):1294-302.
- (34) Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol* 2013 Feb;66(2):173-83.
- (35) Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med* 1999 Feb 15;18(3):321-59.
- (36) Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.
- (37) Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10(1):101-29.
- (38) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003 Sep 6;327(7414):557-60.