TNF-alpha inhibitors for juvenile idiopathic arthritis (Protocol)

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of TNFi in patients with JIA.
BACKGROUND

The pharmacological treatment of pediatric rheumatic diseases aims to prevent impairment of function and joint destruction, as well as improvement of quality of life for patients and their families. Despite the numerous available drugs, the benefits and harms of biological drugs in pediatric patients are still controversial.

Description of the condition

Juvenile idiopathic arthritis (JIA) is a group of rheumatic disorders characterized by onset, without any evident cause, of joint inflammation, persisting for a minimum of six weeks, before the patient’s 16th birthday (Petty 2004). The cardinal clinical feature is persistent swelling of the affected joint(s) with pain. The symptoms of JIA are often initially unspecific, including reduced activity, fatigue, and poor appetite. One of the early signs, particularly in younger children, is limping. Morning stiffness, with improvement later during the day, is common. Other disease features include high fever, skin rash, enthesitis (inflammation of the sites where tendons or ligaments insert into the bone), uveitis (inflammation of the middle layer of the eye), and serositis (inflammation of tissues lining vital organs, such as lungs, heart, and the abdominal organs). Untreated or unresponsive JIA may impair patients’ quality of life and their ability to work and it may lead to permanent disability (Amine 2009; Gutierrez-Suarez 2007; Haverman 2012).

The disease affects 7.5 to 9 out of 100,000 persons a year, giving a prevalence ranging between 62.9 and 78.1 out of 100,000 people (Thierry 2014). The prevalence rate is lower in Asian populations and higher in European countries, with an overall trend of increasing rates (Oberle 2014).

According to the International League of Associations for Rheumatology (ILAR) classification (Petty 2004), JIA affecting one to four joints during the first six months of disease is called ‘oligoarticular’ or ‘pauciarticular’; the form affecting more than four joints during the first six months of disease is called ‘polyarticular’. When the involvement of a larger number of joints occurs after the first six months, the oligoarticular JIA is classified as ‘extended’ or ‘persistent’.

JIA includes seven different subtypes, with oligoarticular and polyarticular JIA being the most common ones.

• Systemic-onset JIA: characterized by arthritis in one or more joints, a fever of at least 2 weeks’ duration, evanescent rash, enlargement of lymph nodes, liver/spleen, and serositis.

• Persistent or extended oligoarticular JIA

• Rheumatoid Factor (RF)-negative polyarticular JIA

• RF-positive polyarticular JIA

• Psoriatic JIA, characterized by arthritis in patients with psoriasis or with at least 2 of the following: dactylitis (inflammation with swelling of a whole finger or toe of unknown cause), nail pitting, onycholysis (detachment of the nail from the nail bed of unknown cause), and/or family history of psoriasis.

• Enthesitis-related JIA, characterized by arthritis or enthesitis (or both) with at least 2 of the following: sacroiliac joint tenderness; the presence of HLA B27 antigen; male over 6 years of age; acute anterior uveitis; history in a first-degree relative of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome, or acute anterior uveitis.

• Undifferentiated JIA, characterized by arthritis that does not fulfill criteria in any of the above categories or that fulfills criteria for 2 or more of the above categories.

The etiology of JIA is largely unknown and the pathophysiology is not clear. It is assumed that the genetic predisposition to JIA is determined by the major histocompatibility complex (MHC) loci. Among MHC loci the HLA-B27 allele has a special position. HLA-B27 antigen is a strong risk factor for the development of enthesitis-related arthritis, and to a lesser extent for psoriatic arthritis and extended course of oligoarthritis (Zuber 2015). As in most autoimmune diseases, interactions between genetic factors, environmental factors, and the immune system lead to a disruption in the immune system homeostasis (state of steady internal physical and chemical conditions maintained by living systems) and to the over-expression of pro-inflammatory cytokines (signaling immune-modulating agents) which result in pathological changes in the joints (Grom 1996).

The clinical diagnosis of JIA is often made when a careful assessment of patient history and a complete physical examination indicate several symptoms and signs of arthritis and associated clinical manifestations that cannot be explained with other known etiologies.

The care of the patients includes active intervention from a whole team that, besides physicians, consists of:

• physiotherapists who check the function of the joints and provide different types of physical treatments and advice. Patients may receive an individually designed program comprising exercise, massage and relaxation;

• occupational therapists who give advice on training when the inflammation affects the hands, wrists and fingers. Patients are provided support for the wrist in the form of soft or hard bandages. For each patient, the occupational therapist also assesses how the environment at home and at school should be adapted to their disease-related needs;

• counsellors/psychologists who provide patients and their parents with support to cope with a difficult life situation because of the illness, as well as with information about social insurance and interactions with social services.

Description of the intervention

The goal of the pharmacological treatment is to prevent joint destruction and function impairment by using the optimal treatment from the earliest stages of the disease. Nowadays, it is still difficult to distinguish, at the time of diagnosis, patients who will require intensive pharmacotherapy from those who have a better prognosis. The recommended treatment of JIA includes non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), and biologic DMARDs (biologics), often used in a pyramidal escalation approach (Beukelman 2011).

NSAIDs (e.g. ibuprofen, naproxen, and diclofenac) are COX (cyclooxygenase)-inhibitors. These drugs are the first-line therapy for the treatment of stiffness and pain in children with JIA. Pain management is also important and sometimes it is necessary...
to add analgesics or physical treatment (or both), such as heat/cold or TENS (transcutaneous electrical nerve stimulation). Local injections of corticosteroids are commonly used to temporarily reduce the inflammation of the synovial membrane, resulting in less joint pain and increased joint mobility.

Among the DMARDs, methotrexate (MTX) is an important cornerstone of the treatment of JIA. MTX is recommended as the first-line treatment in oligoarthritis that persists despite NSAID and intra-articular steroid therapy, and in polyarticular disease (Giannini 1992; Ruperto 2004; Woo 2000). MTX is also recommended in systemic arthritis with predominant joint inflammation, without active systemic features (Ferrara 2018), as well as for the treatment of JIA-related uveitis refractory to topical treatment (Simonini 2013). The results of a placebo-controlled study have provided evidence that sulfasalazine (SSZ) is effective and safe in the treatment of children with oligoarticular- and polyarticular-onset JIA, although it was not well tolerated in one-third of the patients (van Rossum 1998). Nonetheless, neither SSZ nor other DMARDs are approved for the treatment of JIA.

The introduction of biologics in treating rheumatological diseases has provided physicians with a revolutionizing tool that is effective and targets the immune system more selectively. The use of biologics in JIA is indicated when the treatment with one or more DMARDs does not have any effect or when adverse events (AEs) of MTX or other DMARD are not acceptable. Nonetheless, there is an international consensus that polyarthritis with high disease activity and systemic JIA can be treated more aggressively with biologics (Dewitt 2012; Ringold 2014). The use of biologics in combination with MTX or other DMARD may reduce the development of anti-drug antibodies (Ferrara 2018). Aggressive pharmacotherapy may present a risk of serious side effects, however, both in the shorter and the longer perspective. This strategy demands regular monitoring and follow-up.

The data supporting the use of biologics is growing, specifically for tumor necrosis factor-alpha inhibitors (TNFi) (Gutierrez-Suarez 2010). Five different TNFi have been developed to target the binding of this protein and thereby reduce the inflammation: infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab. Just two of these have been approved by the US Food and Drug Administration (FDA) for the treatment of JIA: adalimumab and etanercept. Adalimumab is given subcutaneously every other week. It is approved for the treatment of polyarticular JIA and active enthesitis-related arthritis. Etanercept is given once or twice weekly, subcutaneously. It is approved for the treatment of polyarticular JIA (RF-positive or -negative) from the age of two years, in case of inadequate response or intolerance to MTX. The European Medicines Agency (EMA) has approved the use of etanercept in juvenile patients with extended oligoarthritis, and in adolescents from the age of 12 years affected by psoriatic arthritis and enthesis-related arthritis. Infliximab is a chimeric TNFi that failed to show a statistically significant difference in its primary outcome at three months in a placebo-controlled trial. However, after one year the response to infliximab was comparable to that observed with etanercept. Paradoxically, despite similar efficacy, patients treated with 3 mg/kg of infliximab experienced a greater frequency of serious adverse events and autoantibodies than those given 6 mg/kg (Ruperto 2007). Infliximab is not approved for use in JIA. Golimumab is injected subcutaneously once monthly. Although the primary outcome in the clinical trial was not met, golimumab has been approved in Europe for the treatment of polyarticular JIA, in combination with MTX, in children from two years of age who have not responded adequately to treatment with MTX (Brunner 2018).

Biosimilars are medical products that are highly similar to other already approved biological drugs. Biosimilars to adalimumab, infliximab, and etanercept are approved and are currently in use for the treatment of different rheumatic diseases, including JIA. Further biologics have been approved for the treatment of JIA, such as IL-6 inhibitors (tocilizumab), IL-1 inhibitors (anakinra in Europe, and canakinumab) and T-cell co-stimulation blockers (abatacept), but their use is currently limited to JIA with a systemic or polyarticular course (Brunner 2015; Giancane 2016; Lovell 2015).

Not all children with JIA have experienced a desired complete clinical response to the approved available drugs, however, and have therefore been treated off-label, with other monoclonal antibodies, such as secukinumab (Foeldvari 2019) and rituximab (Kearsley-Fleet 2019). Targeted synthetic DMARDs (tsDMARDs) already approved for the treatment of rheumatic diseases in adults, such as tofacitinib (NCT02592434), baricitinib (NCT03773978), and upadacitinib (NCT03725007) are investigated in refractory JIA and will probably be approved within the next few years.

**How the intervention might work**

JIA and other rheumatological diseases are characterized by a disproportionate activation of the immune system, due to cytokines production by different types of cells. Tumor necrosis factor-alpha (TNF) is one of these cytokines. It induces inflammation, pain, and tenderness in several inflammatory diseases. Numerous studies have found a high concentration of TNF in serum and synovial fluid in children suffering from JIA (Kutukculer 1998; Lepore 1994; Mangge 1995). It is likely that TNF plays a pivotal role in inflammatory cell trafficking into the synovium. The TNFi were developed to block the activation of TNF. Etanercept is a receptor fusion protein that binds to TNF, thus it prevents binding of TNF to the target cell surface. Infliximab is a chimeric (mouse/human) monoclonal antibody of the IgG1k isotype that binds with a high affinity to TNF. Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human TNF. Golimumab is a human monoclonal antibody that binds to both soluble and transmembrane TNF. TNFi have previously been shown to be effective in the treatment of rheumatoid arthritis (RA) (Breedveld 2006; Kay 2008; Koike 2014). TNFi are today widely used in the treatment of JIA, with a number of clinical trials showing promising results in terms of efficacy and safety (Lovell 2008; Lovell 2009; Ruperto 2007).

**Why it is important to do this review**

The addition of biologics in the last decades has revolutionized the treatment of JIA, radically improving the prognosis and the quality of life. However, the growing use of TNFi in clinical practice for the treatment of JIA is mostly supported by extrapolated data from the treatment of chronic arthritis in adult patients (Breedveld 2006; Kay 2008; Koike 2014). Therefore, a systematic review of the available data would provide clinicians with evidence about the efficacy and tolerability of TNFi in JIA.

**OBJECTIVES**

To assess the benefits and harms of TNFi in patients with JIA.
**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include the following types of studies.
- Randomized controlled trials (RCTs).
- Quasi-randomized controlled trials (qRCTs), defined as trials where the method of allocating the investigated patients is not truly random.
- Data from the randomized part of withdrawal trials, defined as trials where the participants receive treatment for a specified time before being randomized to continue either with the active treatment or with placebo.

We will exclude cross-over and cluster RCTs.

We will include studies reported as full text; and unpublished data as awaiting classification.

We will scrutinize published abstracts to identify ongoing studies or unpublished data. There will be no restrictions with regard to publication time and language.

**Types of participants**

Studies including patients less than 18 years of age, affected by any type of JIA diagnosed by a physician, based upon established international criteria: ILAR; American College of Rheumatology (ACR); European League against Rheumatism (EULAR) (Brewer 1977; Petty 2004).

We will exclude studies if less than 90% of the participants are diagnosed with JIA or the mean age of the included patients is above 18 years.

**Types of interventions**

Treatment with any TNFi, either original or biosimilar, for the treatment of JIA is eligible for the present investigation.

Specific comparisons to be made are as follows.
- Any TNFi as monotherapy or combined with MTX vs placebo
- Any TNFi as monotherapy or combined with MTX vs MTX
- Any TNFi as monotherapy or combined with MTX vs NSAID
- Any TNFi as monotherapy or combined with MTX vs other biologics
- Any TNFi as monotherapy or combined with MTX vs tsDMARDs
- Head to head comparison between different TNFi

We will not impose any restrictions with regard to the dose of TNFi. We will apply no restriction on concomitant or additional treatments (e.g. physiotherapy), as long as this is provided for both the intervention and the comparison group.

**Types of outcome measures**

We will use outcomes that are included in the JIA core domain set proposed by the Outcome Measures in Rheumatology (OMERACT) (Morgan 2019). We will use outcome measures that are validated in JIA or in other pediatric rheumatic diseases.

One of the most common measures of clinical improvement in JIA patients is PedACR. It is an outcome measure based on the ACR response criteria in children, focusing on the following items (Giannini 1997).
- Physician global assessment of disease activity
- Parent/patient assessment of overall well-being
- Functional ability
- Number of joints with active arthritis
- Number of joints with limited range of motion
- Erythrocyte sedimentation rate (ESR)

The PedACR50 and PedACR70 are defined as, respectively, a 50% and 70% improvement in the number of tender and swollen joints, as well as a 50% and 70% improvement in at least three, without worsening in more than one of the included items.

In withdrawal trials, the randomization to active treatment or placebo is often done after a shorter period of time, when all the patients are treated with the active drug. The number of flares that occurred after randomization may be used as an alternative measure of response.

The Childhood Health Assessment Questionnaire (CHAQ) is a disease-specific instrument that assesses functional ability in eight domains (dressing, arising, eating, walking, hygiene, reach, grip, and outside activity) of physical function (30 items) for children between the ages of 6 months up to 18 years. Scores in the CHAQ range from 0 to 3, with 3 indicating a worse health state, so a negative change indicates an improvement (Singh 1994). If CHAQ is not reported and other measures of functional ability are used, we will prefer outcomes developed for JIA, such as the Juvenile Arthritis Functional Assessment Scale (JAFAS) (Lovell 1989), the Juvenile Arthritis Functional Assessment Report (JAFAR) (Howe 1991), the Juvenile Arthritis Functional Status Index (JASI) (Wright 1994) and the Juvenile Arthritis Functionality Scale (JAFS) (Filocamo 2007), in the reported order of priority.

Withdrawals can be due to personal reasons, non-compliance or lost to follow-up. Whenever not specified as above, all the withdrawals will be considered as a decision taken by the patients or the parents or the investigators, due to unexpected adverse events, incompatible with the further participation in the trial.

A Serious Adverse Event (SAE) is defined by FDA as any adverse drug event (experience) occurring at any dose that, in the opinion of either the investigator or the sponsor, results in any of the following outcomes (FDA 2014).
- Death
- Life-threatening event
- Hospitalization or prolongation of existing hospitalization (for > 24 hours)
- Substantial disruption of a person's ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important Medical Event (IME), defined as an event that may jeopardize the patient because of permanent impairment of a body function, or permanent damage to a body structure and that may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
We will estimate direct costs related to the treatment, such as the cost of drugs, hospitalization, laboratory tests, and other diagnostic assessments.

We will assess all the major and minor outcomes at an earlier stage (up to 16 weeks) and at two later stages (> 16 weeks to 26 weeks and > 26 weeks to 52 weeks), after a longer duration of treatment. This approach aims at evaluating the efficacy and tolerability of TNFi at different time points, during the first year of treatment. It may help clinicians to answer some relevant frequent questions, for example how fast the clinical improvement can be achieved, how the drugs are tolerated during the first year of treatment, and what kind of patients are prone to respond to therapy with TNFi. Other assessments concerning long-term efficacy and tolerability are beyond the scope of this review.

We will not use the absence of reporting any of these outcomes as a criterion for study exclusion.

**Major outcomes**

- The proportion of patients achieving the PedACR 70 (Giannini 1997)
- Mean values of pain in Visual Analogue Scale (VAS), or Numerical Rating Scale (NRS) or other pain scales (e.g. faces pain scales)
- Mean values of function using CHAQ (Singh 1994), or other measurements of functional ability
- Patient's perception of disease activity (overall well-being) as defined in the trials
- Remission
- Withdrawals due to adverse events
- Serious adverse events

Time points for outcome assessments: 16 weeks or less; more than 16 weeks to 26 weeks; more than 26 weeks to 52 weeks after study entry.

**Minor outcomes**

- Clinical improvement measured by the ACR response criteria: PedACR50 (Giannini 1997). Time points for outcome assessment: ≤ 16 weeks; > 16 weeks to 26 weeks; > 26 weeks to 52 weeks after study entry.
- Health economics concerning the estimation of direct costs of the treatment, namely costs of the drugs, costs for administration in any care unit, costs for the increased number of outpatient visits (compared to standard treatment with other drugs), costs for additional check-ups (blood tests, X-ray and other imaging), as well as costs for additional care due to side effects. When available, we will collect the above items as individual outcomes. We will not estimate the indirect costs. We will not carry out a cost-effectiveness analysis.
- Total adverse events

**Search methods for identification of studies**

**Electronic searches**

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, and Embase Ovid, from inception until the date of final search. Further, we will search the US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov); and the International Clinical Trials Registry Platform of the World Health Organization (www.who.int/ictrp/en).

We will include unpublished data from relevant conferences (such as Paediatric Rheumatology European Society (PReS), ACR, and EULAR).

We will not impose any restrictions on language in the literature search.

See Appendix 1, Appendix 2, and Appendix 3 for the search strategies that we will apply to the selected databases.

**Searching other resources**

We will check reference lists of all primary studies and review articles for additional references. We will search for trial information on relevant manufacturers' websites.

We will check the websites of the following regulatory agencies for reports of adverse events.

- European Medicines Evaluation Agency - EMEA (www.emea.europa.eu)
- UK Medicines and Healthcare products Regulatory Agency (MHRA) pharmaco-vigilance and drug safety updates (www.mhra.gov.uk)

We will search for errata or retractions from included studies published in full text on Ovid Medline and report the date this was done within the review.

**Data collection and analysis**

**Selection of studies**

Two review authors (FA and CBJ) will independently screen titles and abstracts of identified studies for eligibility. We will retrieve the studies in full text if one of the review authors has classified the study as eligible. The same two review authors (FA and CBJ) will independently screen the studies in full text for inclusion, and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, by consulting a third review author (MC or MB). We will exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (PRISMA Group 2009), and 'Characteristics of excluded studies' table.

**Data extraction and management**

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least three studies in the review. Two review authors (FA and CBJ) will independently extract study characteristics from included studies.

We will extract the following study characteristics.
• Methods: study design, the total duration of the study, details of any ‘run-in’ period, number of study centers and location, study setting, and date of the study.

• Participants: number of participants allocated to the intervention and control group, mean age, age range, percentage of females, disease duration, the severity of the condition, diagnostic criteria, type of JIA; inclusion criteria, and exclusion criteria. In the case of multicenter studies, equity factors such as socioeconomic status and place of residence, when reported.

• Interventions: intervention, comparison, concomitant medications, and excluded medications.

• Outcomes: primary and secondary outcomes specified and collected, and time points reported.

• Characteristics of the design of the trial as outlined below in the 'Assessment of risk of bias in included studies' section.

• Notes: funding for the trial, and notable declarations of interest from the authors of the trial.

Two review authors (FA and CBJ) will independently extract outcome data from the included studies. We will extract the number of events and number of participants per treatment group for dichotomous outcomes, and means and standard deviations and number of participants per treatment group for continuous outcomes.

We will note in the ‘Characteristics of included studies’ table if outcome data were not reported in a usable way and when data were transformed or estimated from a graph. We will resolve disagreements by consensus or by involving a third person (MC or MB). One review author (FA) will transfer data into the Review Manager 5 file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

We will use Plot Digitizer to extract, in duplicate, data from graphs or figures. We will extract unadjusted data. For all the outcomes, we will preferentially extract intention-to-treat (ITT) data, if it is reported as both ITT and per protocol.

Where reports include multiple measures of a single outcome our order of preference will be as follows.

• As measures for response to treatment, we will prefer PedACR70 (Giannini 1997), followed by other PedACR (PedACR-30, 50, 90, etc.). In withdrawal trials only, we will use the number of flares and the time to flares that occurred after randomization as an alternative measure of response, whenever PedACR is not reported.

• As measures for improvement in the functional ability, we will use CHAQ (Singh 1994), followed by other outcomes developed for JIA, such as the JAFAS (Lovell 1989), the JAFAR (Howe 1991), the JASI (Wright 1994) and the JASt (Filocamo 2007), in the reported order of priority.

• As a measure of pain, VAS inactivity is our preferred outcome, followed by an overall VAS score, Numerical Rating Scale (NRS) score, and other pain outcomes (e.g. faces pain scale).

• For continuous outcomes, we prefer the mean score at follow-up time over mean change (and SD) if both are reported.

• In case of data reported at multiple time points (e.g. 4, 8 and 12 weeks), we will extract the closest ones preceding the standard time point of assessment (16, 26 and 52 weeks)

• For the estimation of the direct costs, we will sum up the planned cost of drugs, hospitalization, laboratory tests, and other diagnostic assessments in the intervention group and we will compare these with the same kind of cost in the control group.

For serious adverse events and withdrawal due to adverse events, we will report the proportion of participants who report one or more events.

For withdrawals as a proxy for adverse events, we will report the total sum of each.

Main planned comparisons

Our primary comparison will be TNFi combined with MTX versus placebo combined with MTX.

Our other main comparisons will be grouped as follows.

• TNFi combined with MTX vs MTX alone
• TNFi monotherapy or combined with MTX vs other biologics
• TNFi monotherapy or combined with MTX vs tDMARDs
• Head-to-head comparison between different TNFi

Assessment of risk of bias in included studies

Two review authors (MC, GC) will independently assess the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017). We will resolve any disagreements by discussion or by involving another author (MB). We will assess the risk of bias according to the following domains.

• Random sequence generation
• Allocation concealment
• Blinding of participants and personnel
• Blinding of outcome assessment self-reported outcomes and assessor-reported outcomes
• Incomplete outcome data
• Selective outcome reporting
• Other potential biases, including differences in baseline characteristics not explained by inadequate randomization and co-intervention use

We will grade each potential source of bias as high, low or unclear risk, and provide a quote from the study report together with a justification for our judgment in the ‘Risk of bias’ table. We will summarize the ‘Risk of bias’ judgments across different studies for each of the domains listed.

We will consider blinding separately for self-reported and assessor-reported outcomes (e.g. for not blinded outcome assessment, risk of bias may be low for radiographic joint progression, but high for participant-reported pain and function). In addition, we will consider the impact of missing data on key outcomes.

Where information on the risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the ‘Risk of bias’ table.
We will present the figures generated by the ‘Risk of bias’ tool to provide summary assessments of the risk of bias.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the ‘Differences between protocol and review’ section of the systematic review.

Measures of treatment effect

We will analyze dichotomous data as risk ratios (RRs) and present the results with 95% confidence intervals (CIs). We will analyze continuous data as mean differences (MDs) if the same scale is used to measure an outcome, and will present with 95% CIs.

When different scales are used to measure the same conceptual outcome (e.g. disability), we will calculate standardized mean differences (SMDs), with corresponding 95% CIs. SMDs will be back-transformed to a typical scale (e.g. 0 to 10 for pain) by multiplying the SMD by a typical person’s standard deviation (e.g. the standard deviation of the control group at baseline from the most representative trial) (Schünemann 2017b).

In the ‘Effects of interventions’ results section and the ‘Comments’ column of the ‘Summary of findings’ table, we will provide the absolute per cent difference, the relative per cent change from baseline, and the number needed to treat for an additional beneficial outcome (NNTB), or the number needed to treat for an additional harmful outcome (NNTH). For dichotomous outcomes, we will calculate the NNTB or NNTH from the control group event rate and the RR using the Visual Rx NNT calculator (Cates 2008). We will calculate the NNTB for continuous measures using the Wells calculator (available at the Cochrane Musculoskeletal Group Editorial office: musculoskeletal.cochrane.org). (The NNTB or NNTH will be provided only when the outcome shows a clinically important between-group difference.) We will use the minimal clinically important difference (MCID) in the calculation of NNTB or NNTH; we will assume an MCID of 1.5 points in a 0 to 10 point scale for pain. We will not calculate the MCID for CHAQ, as the CHAQ is relatively insensitive to important short-term changes in children with JIA, according to Brunner 2005.

For dichotomous outcomes, we will calculate the absolute per cent change from the difference in the risks between the intervention and control group using GRADEpro and expressed as a percentage (GRADEpro GDT 2015). For continuous outcomes, we will calculate the absolute benefit as the improvement in the intervention group minus the improvement in the control group, in the original units, expressed as a percentage.

For dichotomous data, we will calculate the relative per cent change as the risk ratio minus 1 and expressed as a percentage. For continuous outcomes, we will calculate the relative difference in the change from baseline as the absolute benefit divided by the baseline mean of the control group, expressed as a percentage.

Unit of analysis issues

Where multiple trial arms are reported in a single trial, we will include only the relevant arms, but we will report that there were multiple trial arms in the ‘Characteristics of included studies’ table. If two comparisons from a three-arm trial are relevant, we will combine the two treatment groups, and compare the combined treatment group to placebo in the usual way. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double counting. For dichotomous outcomes, both the sample sizes and the numbers of people with events can be summed across groups. For continuous outcomes, means and standard deviations can be combined using methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Li 2019).

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only or when data are not available for all participants). Where this is not possible, and we think the missing data introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. We will clearly describe any assumptions and imputations to handle missing data and explore the effect of imputation by sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we will calculate the withdrawal rate using the number of patients randomized in the group as the denominator.

For continuous outcomes (e.g. mean change in pain score), we will calculate the MD or SMD based on the number of patients analyzed at that time point. If the number of patients analyzed is not reported for each time point, we will use the number of randomized patients in each group at baseline.

Where possible, we will compute missing standard deviations from other statistics such as standard errors, CIs or P values, according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2019). We will impute standard deviations (e.g. from baseline, graph or other studies in the meta-analysis) if we cannot calculate them.

Assessment of heterogeneity

We will assess clinical and methodological diversity in terms of participants, interventions, outcomes and study characteristics for the included studies to determine whether a meta-analysis is appropriate. This will be conducted by observing these data from the data extraction tables. We will assess statistical heterogeneity with the I² statistic.

As recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2019), the interpretation of an I² value of 0% to 40% might ‘not be important’; 30% to 60% may represent ‘moderate’ heterogeneity; 50% to 90% may represent ‘substantial’ heterogeneity; and 75% to 100% represents ‘considerable’ heterogeneity. We will keep in mind that the importance of I² depends on: (i) magnitude and direction of effects; and (ii) strength of evidence for heterogeneity.

We will interpret the Chi² test with a P value of 0.10 or less indicating evidence of statistical heterogeneity.

If we identify substantial heterogeneity we will report it and investigate possible causes by following the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2019).
Assessment of reporting biases

We will follow the recommendations in section 10.4 of the Cochrane Handbook for Systematic Reviews of Interventions to examine a funnel plot to explore possible small-study biases (Sterne 2017). In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry and relate this to the results of the review. If we are able to pool more than 10 trials, we will undertake formal statistical tests to investigate funnel plot asymmetry.

To assess outcome-reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (www.who.int/ictrp/en) for the 'a priori' trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will undertake meta-analyses only where this is meaningful: that is, if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. We will not pool data from randomized trials and randomized withdrawal trials, whenever the different inclusion criteria may affect the outcome measures. We will perform a random-effects model. The primary analysis for our reviews for all outcomes (PedACR 70, pain, function, patient’s perception of disease activity or well-being, remission, withdrawals due to adverse events and SAE) will include all the studies.

We will base our conclusions only on findings from the quantitative or narrative synthesis, according to Synthesis Without Meta-analysis (SWIM) reporting guideline (Campbell 2020), of included studies for this review.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

- Analysis of patients with different subtypes of JIA (Systemic JIA, oligoarticular JIA, RF-positive polyarticular JIA, RF-negative polyarticular JIA, enthesitis-related JIA, psoriatic JIA, undifferentiated JIA). JIA is a heterogeneous disease, implying the possibility that the outcome of treatment differs according to the baseline clinical phenotype.
- Analysis of TNFi as monotherapy and TNFi as a treatment in combination with other DMARDs. The outcome of treatment may be related to the simultaneous use of other anti-rheumatic drugs.
- Analysis of TNFi-naïve patients vs other. Non-responders to previous treatment with TNFi may represent a subgroup of patients at risk for treatment failure, suggesting the need for treatment with drugs with other mechanisms of action.

We will use the following outcomes in subgroup analyses.

- Clinical improvement measured by the proportion of the patients achieving the Ped-ACR70 response.
- Improvement in function as measured by CHAQ.
- SAE.

We will use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2014); and will caution in the interpretation of subgroup analyses as advised in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2019).

Sensitivity analysis

We plan to carry out the following sensitivity analyses to investigate the robustness of the treatment effect and safety for the main outcomes, such as clinical improvement as measured by PedACR70, remission, as well as withdrawals due to adverse events and SAE.

Selection bias: we will remove the trials that reported inadequate or unclear allocation concealment from the meta-analysis to see if this changes the overall treatment effect.

Detection bias: we will remove the trials that reported inadequate or unclear participant blinding from the meta-analysis to see if this changes the overall treatment effect.

We will perform a sensitivity analysis using a fixed-effects model for self-reported outcomes including only trials at low risk of detection and selection bias.

Interpreting results and reaching conclusions

We will follow the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions, chapter 12, for interpreting results (Schünemann 2017b); and will be aware of distinguishing a lack of evidence of effect from a lack of effect.

We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

Summary of findings and assessment of the certainty of the evidence

GRADE and 'Summary of findings' tables

Two authors (GC and LD) will independently assess the certainty of the evidence for each outcome, using the GRADE tool (GRADEpro GDT 2015). We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence, as it relates to the studies that provide the meta-analyses with data for the chosen outcomes and report the certainty of evidence as high, moderate, low, or very low.

We will resolve disagreements by consensus or by involving a third person (CBJ or MB). We will use methods and recommendations described in section 8.5 and 8.7, and chapters 11 and 12, of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017; Schünemann 2017a; Schünemann 2017b).

We will create four 'Summary of findings' (SoF) tables, as follows.

- SoF table for the RCT/quasi-RCT on the comparison TNFi + MTX versus MTX + placebo
- SoF table for the randomized withdrawal trials on the comparison TNFi + MTX versus MTX + placebo
- SoF table for the RCT/quasi-RCT on the comparison TNFi combined with MTX vs MTX alone
- SoF table for the randomized withdrawal trials on the comparison TNFi combined with MTX vs MTX alone

TNF-alpha inhibitors for juvenile idiopathic arthritis (Protocol)

8

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SoF tables will include the following outcomes.

- PedACR 70
- Pain
- Function
- Patient’s perception of disease activity (overall well-being) as defined in the trials
- Remission
- Withdrawals due to adverse events
- Serious adverse events

Time points for outcome assessment.

- For randomized/quasi-randomized controlled trials: up to 26 weeks (or the nearest time point for which data are available) after study entry
- For randomized withdrawal trials: up to 26 weeks (or the nearest time point for which data are available) after randomization

We will use GRADEpro software to prepare the SoF tables (GRADEpro GDT 2015). We will justify all decisions about the quality of studies using footnotes. We will provide the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH), absolute and relative per cent change, in the Comments column of the SoF table as described in the 'Measures of treatment effect' section above.

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Elements of the Methods section are based on the standard Cochrane Musculoskeletal Group Protocol Template.
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APPENDICES

Appendix 1. CENTRAL
1. MeSH descriptor: [Arthritis, Juvenile] explode all trees
2. (juvenile arthritis* OR JIA):ti,ab,kw
3. #1 OR #2
4. MeSH descriptor: [Tumor Necrosis Factors] explode all trees
5. ((etanercept or etanercept biosimilar or infliximab or infliximab biosimilar or adalimumab or adalimumab biosimilar or golimumab biosimilar or certolizumab or certolizumab biosimilar):ti,ab,kw
6. (tumor necrosis factor*):ti,ab,kw
7. #4 OR #5 OR #6
8. #3 AND #6

Appendix 2. MEDLINE (Ovid)
1. exp Arthritis, Juvenile/
2. juvenile arthritis*.tw.
3. JIA.ti.
4. 1 or 2 or 3
5. exp Tumor Necrosis Factor-alpha/
6. Tumor Necrosis Factor*.tw.
7. etanercept.sh,rn,tw.
8. enbrel.sh,rn,tw.
9. infliximab.sh,rn,tw.
10. remicade.sh,rn,tw.
11. adalimumab.sh,rn,tw.
12. humira.sh,rn,tw.
15. Certolizumab.sh,rn,tw.
17. infliximab biosimilar*.sh,rn,tw.
18. adalimumab biosimilar*.sh,rn,tw.
19. etanercept biosimilar*.sh,rn,tw.
22. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 4 and 22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomized.ab.
27. randomly.tw.
28. placebo.tw.
29. drug therapy.fs.
30. trial.tw.
31. groups.tw.
32. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. exp animals/ not humans/
34. 32 not 33
35. 23 and 34

**Appendix 3. EMBASE Ovid (including EMBASE CLASSIC)**
1. exp juvenile rheumatoid arthritis/
2. juvenile arthritis*.tw.
3. JIA.tw.
4. 1 or 2 or 3
5. exp tumor necrosis factor/
6. Tumor Necrosis Factor*.tw.
7. (etanercept or enbrel or infliximab or remicade or adalimumab or humira or Simponi or Golimumab or Certolizumab or Cimzia or infliximab biosimilar or etanercept biosimilar or adalimumab biosimilar or Golimumab biosimilar or Certolizumab biosimilar).sh, rn, tw.
8. 5 or 6 or 7
9. 4 and 8
10. random$.tw
11. factorial$.tw
12. crossover$.tw
13. cross over.tw
14. cross-over.tw
15. placebo$.tw
16. (double adj blind$).tw
17. (single adj blind$).tw
18. assign$.tw
19. allocate$.tw
20. volunteer$.tw
21. crossover procedure/
22. double blind procedure/
23. randomized controlled trial/
24. single blind procedure/
25. or/10-24
26. 9 and 25

HISTORY
Protocol first published: Issue 8, 2020

CONTRIBUTIONS OF AUTHORS
MC and FA reviewed the literature and wrote the protocol.
GC, MB, CBJ reviewed the literature and commented on and reviewed the protocol.
IP and LD commented on and reviewed the protocol.

DECLARATIONS OF INTEREST
MC has received payment for one lecture in 2016 from AbbVie and payments for development of meeting report and participation fee for ACR Annual meeting in 2019 from Sanofi not related to the present work.
IP received research funding “ALF funding” (Lund University) and FORTE (a national research council in Sweden) as well as reimbursement and fees for reviewing research grant proposals from the Norwegian Research Council, the Syksonen Lundgren Foundation, Malmö, the Kockska Foundation, Trelleborg, Sweden and the National Research Council for the Swedish National Insurance Agency. He also receives reimbursement for a national project on National guidelines for musculoskeletal disorders through the Swedish National Board of Health and Welfare.
LD reports research grants from BMS and personal fees for lectures/consultation from Janssen, UCB, Galderma, MSD, Eli Lilly, outside the submitted work.

GC has received fee from Novartis for development of educational presentations. GC is the head of the Clinical Trial Unit at Skane University Hospital in Malmo and therefore he is involved as investigator in RCTs funded by different drug companies. His institution gets paid for this.

FA: none known

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CBJ: none known

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**External sources**
- No sources of support supplied