Supplementary Protocol 1

OBJECTIVES

Primary

1. To determine the overall treatment effect up until week 12 of Th17 pathway inhibitors on ACR20 in adults with active psoriatic arthritis (PsA) compared to placebo or active control.

Secondary

2. To determine the overall treatment effect up until week 24 of Th17 pathway inhibitors on ACR20 in adults with active psoriatic arthritis (PsA) compared to placebo or active control.
3. To determine the overall treatment effect up until week 12 or 24 of Th17/ pathway inhibitors on ACR50, ACR70 in adults with active psoriatic arthritis (PsA) compared to placebo or active control.
4. To determine the overall risk of Th17 related adverse effects of interest namely infections, candida infections, tuberculosis and serious adverse events compared to placebo at the end of placebo-controlled period
5. To determine the overall tolerability of Th17 pathway inhibitors by assessing the overall risk of treatment discontinuation due to drug related adverse events compared to placebo at the end of placebo-controlled period.

Research Question in PICO-T framework

The patient population should be representative of adults with active psoriatic arthritis (≥18 years old) of any sex, ethnicity, geographical location, fulfilling classification criteria for Psoriatic arthritis (CASPAR) (8), who have active disease defined as three or more tender joints (out of 68 or 78) and three or more swollen joints (out of 66 or 76), despite previous treatment with nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs (including methotrexate), or TNF inhibitors.

The interventions will include Th17 pathway inhibitors namely Secukinumab, Ixekizumab (IL17A inhibitors), Brodalumab (IL17 receptor inhibitor), Ustekinumab (inhibitor of the common p40 subunit of IL12/23), Guselkumab and Tildrakizumab (IL23 inhibitors).

The control treatments include placebo and/or active control (which were Disease modifying anti-rheumatic drugs (DMARD) such as methotrexate and biologic agents targeting TNF-alpha inhibitors such as adalimumab). Background oral steroid medications and/or NSAIDs (non-steroidal anti-inflammatory drugs) will be permitted if they were prescribed at a stable dose of <=10 mg/ day with no dose modifications permitted during the trial unless it was for safety reasons.

The outcomes of interest are efficacy and safety outcomes. Efficacy endpoints will include clinical improvement in disease activity as indicated by ACR20, -50, and -70 clinical responses reported at 12 weeks and 24 weeks (intention to treat). Studies with efficacy endpoints analyzed for per protocol study population will not be included. Safety endpoints studies will include

related adverse events of interest namely infections, candida infections, tuberculosis, serious adverse events and adverse events that lead to treatment discontinuation.

Time period - All articles published till 16th November 2016 were reviewed and eligible articles will be included in the final meta-analysis per process described in the methods section.

Research question for primary outcome: In adult patients with active psoriatic arthritis, are Th17 pathway inhibitors overall superior (IL-17A, IL17A receptor, IL12/23 and IL23 inhibitors), compared to placebo or active control in producing a higher proportion of ACR 20 responders at 12 weeks of treatment?

Hypothesis for primary outcome: In adult patients with active psoriatic arthritis Th17 pathway inhibitors overall are superior when compared to placebo or active control in producing a higher proportion of ACR 20 responders at 12 weeks of treatment.

METHODS

This systematic review and meta-analysis will be undertaken according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (9).

Search Strategy

The global search strategy will be constructed using the PICO variables as specified in this review`s research question (Supplementary Table 2). Studies published during this period will be evaluated for eligibility and included as appropriate. The review will consider randomized controlled trials (RCT) published in any language excluding single ascending dose studies/phase 1a studies.

Information sources/Databases

The following sources will be systematically searched for relevant studies published till 16th November 2016:

Electronic databases

1. Electronic database: SCOPUS (Medline, EMBASE and Compendex)
2. www.clinicaltrials.gov

All references of retrieved articles will be scanned for further studies.

Eligibility criteria

Inclusion criteria

Criteria for inclusion in this review using the PICO framework is outlined in Supplementary Table 2. In addition, only randomized controlled trials (phase 1a/single ascending dose studies will be excluded) will be considered for the systematic review and meta-analysis. Only studies reporting intention to treat data will be included.

Eligibility criteria

Participants (P)	Intervention (I)	Comparator (C)	Outcome(s)
Inclusion criteria			

Adults (≥18 years old) of any sex, ethnicity, geographical location, fulfilling classification criteria for Psoriatic arthritis (CASPAR), and had active disease, which was defined as three or more tender joints and three or more swollen joints, despite previous treatment with nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, or TNF inhibitors. Patients may or may not have received biologics before but both patient populations will be	• Secukinumab (75 or 150 or 300 mg sc or 10 mg/kg iv) or • Brodalumab (140/210/280 mg) or • Ustekinumab (45 or 90 mg) or • Ixekizumab (80 mg) or • Tildrakizumab or • Guselkumab of any dosage, administered in any injectable form (subcutaneous administered as autoinjector or PFS or intravenous infusion or bolus	• Placebo injections could be combined with usual treatment (+/- Disease modifying anti-rheumatic drugs (DMARD) such as methotrexate and biologic agents targeting TNF-alpha inhibitors such as adalimumab) (DMARDs/TNF-alfa inhibitors/other active agents used per label) or other usual care or any other non-drug intervention(s).	Primary outcome • Disease activity control/improvement as assessed by: ACR20 score at week 12. Secondary outcomes: • Disease activity control/improvement as assessed by ACR 20, 50, 70 at week 12 and 24. Safety outcome • Any infections (including serious infections). • Serious adverse events. • AEs leading to

included in this meta-analysis.	injection) for a minimum of 2 doses (multiple dose studies only) in any dosing regimen.		treatment discontinuation.
Exclusion criteria			
• Patients having any other type of arthritis other than psoriatic arthtirs such as rheumatoid arthritis, ankylosing spondylitis,	• Studies not randomizing a Th17 pathway inhibitor in one arm.	• None	• Studies not reporting ACR 20 at 12/24 weeks. • Per protocol analysis of ACR20 response at week 12/24 will be

osteoarthritis etc., pregnancy, phase-1 studies (single ascending dose studies).			excluded.

*ACR20, American College of Rheumatology response criteria; IL-17, interleukin-17; Il-23, Interleukin-23

Table: Concept for search strategy

Concept for search strategy		
Step 1	Concept 1 **Th17 pathway inhibitors**	Concept 2 **Psoriatic Arthritis**
Step 2	IL17A inhibitors, secukinumab, ixekizumab, IL17R blockers, brodalumab, IL12/23 inhibitors, ustekinumab, IL23 inhibitors, tildrakizumab, guselkumab	psoriatic arthritis, PsA, active psoriatic arthritis, psoriatic arthropathy,
Step 3	#1 = IL17A inhibitors OR secukinumab OR ixekizumab OR IL17R blockers OR brodalumab OR IL12/23 inhibitors OR ustekinumab OR IL23	#2 psoriatic arthritis OR PsA OR active psoriatic arthritis OR psoriatic arthropathy

	inhibitors OR tildrakizumab OR guselkumab	
Step 4	#1 AND #2	

* Only randomized controlled clinical trials will be considered for inclusion (phase 1 studies are excluded)

Full electronic search strategy for SCOPUS; Limiters: Till November 16th 2016, articles, abstracts or reviews. No language restrictions will be applied.

SCOPUS search terms: (Articles published till 16 NOV 2016)

((TITLE-ABS-KEY (il17a inhibitor*) OR TITLE-ABS-KEY (il17a blocker*) OR TITLE-ABS-KEY (il17r inhibitor*) OR TITLE-ABS-KEY (il17r blocker*) OR TITLE-ABS-KEY (il12/23 inhibitor*) OR TITLE-ABS-KEY (il12/23 blocker*) OR TITLE-ABS-KEY (il23 inhibitor*) OR TITLE-ABS-KEY (il23 blocker*) OR TITLE-ABS-KEY (secukinumab*) OR TITLE-ABS-KEY (ixekizumab*) OR TITLE-ABS-KEY (brodalumab*) OR TITLE-ABS-KEY (ustekinumab*) OR TITLE-ABS-KEY (tildrakizumab*) OR TITLE-ABS-KEY (guselkumab))) AND (ALL (psoriatic arthritis*) OR TITLE-ABS-KEY (psa*) OR TITLE-ABS-KEY (psoriatic arthropathy)) AND ((TITLE-ABS-KEY (trial*)) OR (TITLE-ABS-KEY (random*)) OR (TITLE-ABS-KEY (phase*)))

Procedure for selection of studies

The initial search for studies by titles and abstracts will be conducted independently by two reviewers (GN, WKM). All studies identified as potentially relevant to the review question will

be eligible for full text review. Retrieved studies will be exported and duplicates screened. The study selection process will be summarized per PRISMA flowchart framework.

Data extraction and management

Two reviewers will independently complete data extraction (GN, CE) from the included studies to a pre-designed form in Microsoft Office Excel. Data to be extracted from each study will include author names, publication date, country where study was conducted, baseline demographic characteristics and disease classification/severity, previous exposure to other drug therapies (nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs, or TNF-alpha inhibitors), intervention (drug name, dosage, route of administration and duration) active treatment details, and placebo, and whether study is a phase 2 or 3, 4 or post registration trial.

Lastly, we will collect information on treatment outcomes (both primary and secondary) and any reported related adverse events of interest namely infections, candida infections, tuberculosis, serious adverse events and adverse events that lead to treatment discontinuation to assess tolerability. Extracted data will includ mean values and SDs (or medians and IQR) of the outcomes, and their respective confidence intervals where applicable; frequency counts and/or proportions for dichotomous variables; point estimates and their associated dispersion measures; number of participants (in each study arm), intention-to-treat analysis (per protocol analysis will be excluded) and the p-values.

List and definition of all variables for which data will be sought.

<u>Patient population (P)</u>

Active PsA and moderate to severe disease definitions: For a patient to qualify as having active PsA defined per CASPAR 2006 criteria, (8) at baseline ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 must be demonstrated clinically for satisfying the criteria of active PsA. All biologic trials are performed/indicated for moderate to severe disease to balance the risk benefit ratio. Moderate to severe disease is indicated by measuring baseline DAS28-CRP (Disease Activity Score in 28 joints) - C Reactive Protein. DAS28-CRP < 2.6 is considered as remission while a score >=2.6 - <3.2 is considered as mild disease. A score of ≥ 3.2 – 5.1 is categorized as moderate and a score of ≥ 5.1 is categorized as severe disease. (10) It is more difficult to establish treatment difference in mild disease and hence all trials are performed in moderate to severe active PsA in addition to the risk benefit balance.

CASPAR criteria as defined in Taylor et al., 2006 (8)

"To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist. A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.

A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.

2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.

3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.

5. Radiographic evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot." (8)

Intervention (I)

Th17 blocking agents/inhibitors: refers to biologics targeting cytokines or receptors for cytokines in the Th17 pathway such as interleukin 17A, IL17R, IL23 and IL12/23 (Refer rationale in Page 1 for details; Mease et al., 2015). (11)

Secukinumab: is a fully human monoclonal antibody against interleukin 17A. (11)

Ixekizumab: is a humanized monoclonal antibody against interleukin 17A. (11)

Brodalumab: is a human monoclonal antibody against interleukin 17 receptor (R). (11)

Ustekinumab: is a human monoclonal antibody against the common p40 subunit of interleukins 12 and 23 and referred to as blocker of IL-12/23. (11)

Guselkumab: is a human monoclonal antibody against interleukin 23. (11)

Tildrakizumab: is a humanized monoclonal antibody against interleukin 23. (11)

Placebo medication

Placebo medication was placebo injections, which could be combined with active treatment or other usual care.

The active treatment could be Anti-TNF agents and DMARDS.

Anti-TNF agents: refers to biologics inhibiting TNF-alpha, a key Th1 cytokine involved in inflammation and has been implicated in the pathogenesis of several autoimmune disorders such as Rheumatoid Arthritis and Psoriatic Arthritis. These are Adalimumab, Etanercept or Infliximab (Ali et al., 2013). (12)

DMARDs: Disease Modifying Anti-Rheumatic Drugs are disease modifying drugs prescribed for modifying the course of disease conditions such as rheumatoid, psoriatic and other arthritic diseases with an inflammatory pathogenesis. These include drugs such as methotrexate, hydroxychloroquine, sulfasalazine. These are used as first line treatment options in low doses for mild psoriatic arthritis and rheumatoid arthritis. (13)

NSAIDs: Non-steroidal anti-inflammatory drugs are drugs prescribed for the symptomatic relief of pain. These commonly target the enzymes in the cyclooxygenase pathway (COX). Common drugs include ibuprofen, naproxen, diclofenac etc. (13)

Steroids: in the context of this meta-analysis refers to immune suppressing glucocorticoids. (14)

Outcome: American College of Rheumatology (ACR) response of ACR20, 50 and 70: ACR core criteria is composite endpoint computed by measuring swollen joint count (SJC), tender joint count (TJC) and five other components of ACR core criteria: Health Assessment Questionnaire – Disability Index (HAQ-DI), PGA (Physician's Global Assessment of Disease Activity) on a Visual Analogue Scale (VAS) of 0 – 100 mm, Patient Assessment of Pain on a VAS of 0-100 mm, C Reactive Protein and Patient Assessment of Disease Activity on a VAS of 0 – 100 mm. A

20% improvement in SJC, TJC and at least three of the 5 components enumerated above represents an ACR 20 response and is accepted as a clinically meaningful and an internationally accepted regulatory endpoint for clinical trials designed to seek regulatory approval. ACR50 and 70 represents similarly a 50 and 70% improvement from baseline. (15)

Note: For this meta-analysis ACR20 will be extracted for week 12 – irrespective of whether study primary endpoint was week 12 or 16 or 24. For studies where ITT effect is not reported, they will be excluded from inclusion.

Meta-regression covariates: DAS28-CRP – defined above (refer second paragraph of patient population; Wells et al., 2009). (10)

PASI – Psoriasis Area Severity Index is a composite score which measures psoriasis disease activity. (16,17)

Risk of bias (quality) assessment of included studies

The Cochrane risk of bias tool - a validated and internationally acknowledged instrument will be employed to evaluate the methodological quality of each included study. (18) This assessment will be independently done by three reviewers (IM, SD, BAW) and WKM will serve as the adjudicator for resolving disagreements. Each trial included will be reported to have low, uncertain or high risk of bias. This assessment will be based on the evaluation of the random sequence generation, allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias.

Summary measures and approach for data synthesis of results and analysis

We will report the relative risk along with the 95% CI for the primary and secondary dichotomous outcomes namely, ACR20, 50, 70, drug related infections (including serious infections), serious adverse events and adverse events that led to treatment discontinuation.

We will perform all statistical analyses using STATA 13.0 (STATACorp, 2013). (19) Bias assessment will be performed using Review Manager (RevMan) Software 5.3 (RevMan, 2014). (20) We will use random effects model (DerSimonian and Laird) as we anticipate considerable differences in terms of drug mechanisms within the Th17 class which includes a variety of strategies of modulating this pathway.

Heterogeneity analysis

We will assess statistical heterogeneity with forest plots subtracting each study at a time. The between study variance will be reported using I^2-statistical analysis, where values of 25%, 50% and 75% will be taken as cut-off points for low, moderate and high degrees of heterogeneity, respectively. We will also assess heterogeneity by Cochrane Q statistic test and report corresponding p-values. Sources of heterogeneity will be explored through subgroup analyses according to study-level characteristics including (1) phase 2 vs. phase 3, 2) primary vs. secondary endpoint and (3) prior exposure to biologics (biologic/TNF naïve or biologic/TNF experienced).

Meta-regression

We will perform meta-regression to estimate if the differences in RR between studies can be explained by study differences. We will use the relationship for placebo baseline characteristics as the groups are expected to be comparable with respect to baseline characteristics: mean age, percentage of males, percentage of whites, mean body weight, mean body mass index,

percentage use of methotrexate, history of TNF inhibitor use, mean DAS28-CRP and mean PASI score on the primary outcome of ACR20 at week 12 and secondary outcome of week 24.

Assessment of publication bias

Presence of publication bias will be examined by plotting funnel plots. This will be complemented with formal statistical testing by use of Egger's and Begg's tests. The robustness of the findings of publication bias will be assessed by Duval and Tweedie's trim and fill methods.

Ethical considerations

Formal ethical clearance is not warranted as the review uses secondary non-confidential data from published/unpublished studies. Further, as a review, it does not directly involve any direct intervention with patients.

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