Materials and Methods

This systematic review and meta-analysis were undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework [10]. The checklist is provided in the protocol section. A formal protocol was developed internally by the study team prior to performing the meta-analysis (see suppl. protocol 1).

Search Strategy

The global search strategy was constructed using the PICO variables (suppl. Tables 1 and 2, and suppl. protocol 1). Studies published were evaluated for eligibility and included as appropriate. The review considered randomized controlled trials published in any language excluding single ascending dose studies/phase 1a studies. The following sources were systematically searched for relevant studies published till November 16, 2016: the electronic database SCOPUS (Medline, EMBASE, and Compendex) was used to search all published articles, and www.clinicaltrials.gov was used for searching clinical trials registered for drugs of this class. All references of retrieved articles were scanned for further studies.

Eligibility Criteria

Randomized controlled trials (phase 1a/single ascending dose studies were excluded) were considered for this systematic review and meta-analysis. Only studies reporting intention-to-treat effect estimates were included: adults (≥18 years old) of any sex, ethnicity, geographical location, fulfilling classification criteria for psoriatic arthritis (CASPAR) [11] and who had active disease, which was defined as 3 or more tender joints and 3 or more swollen joints, despite previous treatment with nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, or TNF-α inhibitors. Patients may or may not have received biologics before.

The intervention included Th17 pathway inhibitors: secukinumab (75 or 150 or 300 mg s.c. or 10 mg/kg i.v.) 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 (subcutaneously administered by autoinjector or prefilled glass syringe or intravenous infusion or bolus injection) for a minimum of 2 doses (multiple dose studies only) in any dosing regimen. Doses and regimens varied across studies, and we combined different doses and regiments for each Th17 inhibitor. Firstly, because there were limited studies to analyze for specific doses, and secondly, since we combined lower and higher doses uniformly across all agents, we expected that the overall treatment effect estimate compared to placebo would not change in direction although the effect could be diluted or averaged.

The comparator was either placebo or active control. Placebo injections could be combined with usual treatment (with or without DMARD such as methotrexate and biologic agents targeting TNF-α such as adalimumab or etanercept) and other active agents used per label or any other nondrug interventions.

Procedure for Selection of Studies

The initial search for studies by titles and abstracts was conducted independently by 2 authors (G.N., W.K.M.). All studies identified as potentially relevant to the review question were eligible for full-text review. Retrieved studies were exported, and duplicates were screened. The study selection process has been shown in a PRISMA flowchart (Fig. 1).

Data Extraction and Management

Two authors independently completed data extraction (G.N., C.E.) from the included studies to a predesigned form in Microsoft Office Excel. Data to be extracted from each study included but were not limited to 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 antirheumatic drugs, or TNF-α inhibitors), intervention (drug name, dosage, route of administration, and duration), active treatment details, and placebo, and whether the study was a phase 2 or 3 or postregistration trial.

Lastly, we collected 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, and treatment discontinuation due to adverse events or intolerance to assess tolerability. Extracted data included: mean values and standard deviations (or medians and interquartile ranges) 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 and the *p* values.

Risk of Bias (Quality) Assessment of Included Studies

The Cochrane risk of bias tool – a validated and internationally acknowledged instrument – was employed to evaluate the methodological quality of each included study [12]. This assessment was independently done by 3 reviewers (I.M., S.D., B.A.W.), and W.K.M. served as the adjudicator for resolving disagreements. Each trial included was reported to have a low, uncertain, or high risk of bias. This assessment was 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.

Statistical Analysis

Summary Measures and Approach for Data Synthesis of Results and Analysis

We calculated the pooled relative risk (RR; likelihood) of having a beneficial treatment effect along with the 95% CI for the primary and secondary dichotomous outcomes, namely ACR20, ACR50, ACR70, and the pooled RR for having any drug-related infections (including serious infections), serious adverse events and adverse events that led to treatment discontinuation. We used a random effects model (DerSimonian and Laird) to allow a distribution of true effect sizes due to study differences.

We performed most statistical analyses using STATA 13.0 (STATA Corp., 2013) [13]. Bias assessment was performed using Review Manager (RevMan) software 5.3 (RevMan, 2014) [14]. The statistical program Comprehensive Meta-Analysis was used to double-check results, for fill and trim analysis, and removing 1 study at a time. A p value <0.05 was considered statistically significant.

We assessed statistical heterogeneity with forest plots subtracting each study at a time. The between-study variance was reported using I^2 statistical analysis, where values of 25, 50, and 75% were taken as cutoff points for low, moderate, and high degrees of heterogeneity, respectively. We also assessed heterogeneity by the Cochrane Q statistic test and reported corresponding p values. Sources of heterogeneity were explored by subgroup analyses per study level characteristics including phase 2 versus phase 3, primary versus secondary end point, mechanism of action (IL-17A, IL-17RA, and IL-12/23p40), and TNF-α naivety.

We performed meta-regression to estimate whether the differences in log RR (y-axis) between studies could be explained by continuous baseline characteristics (x-variable). Since groups are balanced in the studies, we decided to use the relationship for placebo baseline if the following variables were reported in 5 or more studies: mean age, percentage of males, percentage of whites, mean body weight, mean body mass index, percentage use of methotrexate, mean Disease Activity Score in 28 joints/C-reactive protein (DAS28-CRP) and mean Psoriasis Area Severity Index (PASI) score on the primary outcome of ACR20 at week 12.

Presence of publication bias was examined by funnel plots and by formal statistical testing by (a) Egger's test of the intercept (from a model using precision (the inverse of the standard error) to predict the standardized effect (effect size divided by the standard error)), (b) Begg's rank correlation test (computing the rank order correlation (Kendall's τ b) between the treatment effect and the standard error (primarily driven by sample size)), and by Duval and Tweedie's trim and fill method to determine where missing studies are likely to fall, and to add them to the analysis, and then recompute the combined effect based on a random effects model.