Comparative effectiveness associated with use of biologics and small-molecules for psoriasis: Protocol for a systematic review and meta-analysis

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Background: Many patients with psoriasis (PsO) have (or will develop) psoriatic arthritis (PsA), a chronic inflammatory disorder involving joints, entheses, bone, axial skeleton, and skin - heterogeneous clinical features associated with substantial disability and reduced life expectancy. It is not known whether early and/or intense treatment of PsO/PsA can prevent disease progression and whether identifying and treating all patients intensively is beneficial (and safe) in the long term.

The advent of biologic drugs and new oral treatments (i.e., small molecules) has increased the number of treatment options for patients with PsO (and PsA) who are candidates for systemic therapy.

Rationale: Despite the apparently very costly pricing of biologics and small-molecules, these therapies are important to some PsO patients, as they are critical to good disease management in individuals with severe/refractory disease. It is important that decision-makers are fully aware of all the ‘pros and cons’ associated with different treatment options, and strive for prescribing the drug with the best comparative effectiveness.

Objective(s): After a systematic review of randomised controlled trials, we will perform evidence-synthesis to evaluate how the different targeted therapies compare in terms of benefit and harm in adults with PsO and/or PsA.

Design: Systematic review and meta-analysis inferring from both direct and indirect evidence based on network meta-analyses of randomised trials.

Eligibility criteria: The inclusion criteria for study selection will be randomised controlled trials; patients diagnosed with PsO and/or PsA; trials reported in English, Danish, Swedish, or Norwegian; trials consisting of a minimum of two arms at least one receiving an approved targeted therapy; studies including only adults (≥18 years). Targeted therapies of interest currently include the following agents approved (EMA) for PsO:

- Humira (adalimumab),
- Enbrel (etanercept),
- Remicade (infliximab),
- Cosentyx (secukinumab),
- Stelara (ustekinumab);

And, a new oral therapy

- Otezla (apremilast).

**Information sources and search:** Trials on biologics and small-molecules for PsO and/or PsA will be reviewed using the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and MEDLINE (via PubMed) from database inception. The results of registered unpublished completed studies will be procured through abstract publications or poster presentations.

**PUBMED**


**COCHRANE**

Search

#1 MeSH descriptor: [Recombinant Fusion Proteins] explode all trees
#2 MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#3 MeSH descriptor: [Receptors, Tumor Necrosis Factor] explode all trees
#4 MeSH descriptor: [Monokines] explode all trees
#5 monoclonal antibody ca2
#6 TNFR-Fc fusion protein
#7 etanercept
#8 enbrel
#9 infliximab
#10 remicade
#11 Inflectra
#12 Remsima
#13 adalimumab
humira
#15  D2E7
#16  idec c2b8
#17  golimumab
#18  simponi
#19  ctno-148
#20  certolizumab
#21  CDP870
#22  cimzia
#23  "TNFR:Fc":ti,ab,kw (Word variations have been searched)
#24  tofacitinib:ti,ab,kw (Word variations have been searched)
#25  MeSH descriptor: [Janus Kinases] explode all trees
#26  Xeljanz:ti,ab,kw (Word variations have been searched)
#27  MeSH descriptor: [Phosphodiesterase 4 Inhibitors] explode all trees
#28  Ustekinumab
#29  CNTO-1275
#30  Stelara
#31  MeSH descriptor: [Interleukin-23] explode all trees
#32  MeSH descriptor: [Interleukin-12] explode all trees
#33  MeSH descriptor: [Interleukin-17] explode all trees
#34  Secukinumab
#35  AIN457
#36  Cosentyx
#37  apremilast
#38  Otezla
#39  CC-10004
#40  #1 or #2 or #3 or #4 or #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 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39
#41  MeSH descriptor: [Psoriasis] explode all trees
#42  MeSH descriptor: [Arthritis, Psoriatic] explode all trees
#43  Psoria*
#44  #41 or #42 or #43
#45  #40 and #44
#46  #45 in Trials

**Clinicaltrials.gov**

*Study Type (Interventional); Conditions (Psoriatic OR Psoriasis); Interventions (adalimumab OR D2E7 OR certolizumab OR CDP870 OR etanercept OR TNFR:Fc OR golimumab OR CNTO148 OR infliximab OR tofacitinib OR CP-690,550 OR apremilast OR CC-10004 OR Secukinumab OR AIN457 OR CNTO-1275 OR Ustekinumab).*

**Study selection:** We will include randomised trials of PsO and/or PsA in adults who were treated with any of the drugs (five biologics and apremilast) approved for the treatment of PsO, alone or in combination; if
any of these drugs were compared with each other, placebo, or traditional DMARDs (incl. DMARD combinations) the study will be considered eligible.

Data collection process, outcomes and endpoints: For benefit outcome, we will capture information on the number of PASI75, PASI90, and ACR20 (if possible). For harm outcome, we will extract data on the number of withdrawals due to adverse events, and the number of serious adverse events. As a measure of “tolerability” we will use the number of patients who completed the trial period (according to our specified endpoint). The dermatology life quality index (DLQI) will be used to assess the aspects of disease on daily living.

Our primary endpoint will be the last observed time point in the trial, before allowed dose escalation or treatment cross-over; patients with escalated dose and patients that have crossed over are no longer comparable to patients on a fixed dose treatment in terms of estimating efficacy and safety.

For each trial, we collected (1) type of intervention(s) - including dose, categorised according to the product labelling as recommended - below recommended (low) or above recommended (high); (2) type of comparator(s); (3) study duration (i.e., longest controlled period); and (4) total person years for each treatment group (if not reported, it will be estimated by assuming a linear dropout rate between baseline and end of controlled period).

Risk of bias assessment: The influence of study quality and potential risk of bias among the eligible trials will be included in the meta-analysis for the purpose of sensitivity using stratified analyses. We will assess the following study limitations, also referred to as key domains: 1) randomisation followed by concealment of treatment allocation, 2) blinding of participants and health care professionals, and 3) adequacy of statistical analyses (i.e., proper use of the intention-to-treat [ITT] population).

We will conduct stratified analyses and meta-regression to investigate whether associations vary according to type of targeted therapy, study design (standard vs adaptive trial design), indication (PsO vs PsA vs Mixed population), comparator (active vs placebo), and duration of follow-up at endpoint (i.e., covariate measured in weeks). Statistical analyses will be performed using Review Manager (version 5.3) and SAS statistical software (version 9.4).

GRADE (Grading of Recommendations Assessment, Development and Evaluation) will be used to rate the overall quality of the evidence for risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect. The GRADE ratings of very low-, low-, moderate-, or high-quality evidence reflect the extent to which we are confident that the effect estimates are correct.

Synthesis of results: Through integrated analyses of published literature, we will calculate the absolute benefit and harm for the available efficacy and safety measures corresponding to the approved dosing regimens of the eligible drugs.
For the direct (head-to-head comparisons) evidence, we will compute standard meta-analysis estimates based on the contrast between groups with 95% confidence intervals in either of the two conditions. These estimates will be combined using meta-analysis methodology. We will test for heterogeneity with the Cochran’s Q-test and use the method proposed by Higgins et al to measure inconsistency ($I^2$). We will apply inverse variance random effects for meta-analysis, whereas the fixed-effect analysis will be applied to explore the likelihood of small-study bias (i.e., sensitivity). These estimates are referred to as ‘Direct estimates’.

In order to combine both direct and indirect evidence we will apply a hierarchical model (generalized linear mixed model) using a collection of trials of alternative interventions for PsO and/or PsA that allow, through direct and indirect comparisons, calculation of the relative effects of all treatment versus placebo or standard care, and versus one another, on a particular outcome. These estimates are referred to as ‘Network meta-analysis estimates’.

**Judging values and preferences:** Making trade-offs between desirable and undesirable consequences of alternative management strategies, incl. different routes of administration (i.v., s.c., p.o.) — the fundamental process of making recommendations—requires making value and preference judgments. For psoriasis therapy guidelines, this trade-off involves, in most instances, an anticipated substantial reduction in disease activity maybe compared with a more modest effect, when the latter treatment option is easier (i.e., more feasible) to the patient. Ideally, the values and preferences applied to this decision would be the average values and preferences of the patient population.

We know, however, that patient values for health outcomes vary substantially from patient to patient. Knowledge of the extent to which patient values and preferences vary is one factor in deciding on the strength of a recommendation. The greater the variability in values and preferences, the more likely a weak recommendation is appropriate. To inform these decisions, we surveyed existing literature bearing on patient values and preferences regarding route of administration by asking all the pharmaceutical companies as well as the Danish Psoriasis Association (i.e. stakeholders) to provide us with key literature that would help us address this topic.

**Ethics and dissemination:** As no primary data collection will be undertaken, no additional formal ethical assessment and informed consent are required. Using data from randomised trials, this study will evaluate different targeted therapies for PsO and/or PsA patients. Our review will present data for all approved (EMA) targeted therapies, in terms of comparative effectiveness, and evaluate the quality of the evidence using the recommendation from the GRADE working group.

Our dissemination goal is to help clinicians make evidence-based decisions and help international guideline developers with an updated evidence synthesis, which will enable a comprehensive interpretation of the data for benefit and harm in both PsO and/or PsA including the likely combination.
This systematic review and meta-analysis will help facilitate evidence-based management, and identify key areas for future research in PsO (and indirectly relating to PsA). Following the systematic review and meta-analysis, recommendations will be generated according to the principles recommended from the GRADE working group, based on the consensus judgment of clinical experts from a wide range of disciplines, informed by available evidence, balancing the benefits and harms, and incorporating patient’s and clinician’s preferences and values. We expect that these recommendations will be utilized by health care providers in Denmark, and globally will inspire health care providers involved in the management of patients with psoriasis.

Protocol registration: PROSPERO CRD42015029122

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