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Assessing the importance of trial characteristics as contextual factors when evaluating targeted therapies in patients with psoriatic disease: Protocol for an exploratory systematic review and meta-research project

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ABSTRACT

Rationale: Over the last decades, the management of psoriatic arthritis (PsA) and psoriasis has markedly improved, especially due to the introduction of targeted therapies (biological disease modifying anti-rheumatic drugs [bDMARDs] and new oral targeted synthetic DMARDs [tsDMARDs]). Trial eligibility criteria and patient baseline characteristics vary in randomised controlled trials (RCTs) testing targeted therapies. However, little is known about how these differences in study setting (contextual factors) influence the treatment effect.

Objectives: To assess the importance of various trial and patient demographic baseline characteristics as contextual factors when evaluating treatment effect of targeted therapies for patients with PsA and psoriasis.

Methods: In this systematic review and meta-analysis, we will identify RCTs by searching electronic databases and scanning reference lists of retained articles. The following databases will be used for the search: Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and MEDLINE (via PubMed). Patients should be adults (≥ 18 years) and have a diagnosis of PsA and/or psoriasis. The interventions of interest will be targeted therapies with a standard route of administration and dosages approved by the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) for treating PsA and/or psoriasis.

Data synthesis: Data synthesis will assess outcome data at 3 – 6 months. We aim to analyse the treatment effect of the targeted therapies in the two diseases, PsA and psoriasis, in combination by using a common outcome, "*retention",* and separately by using the American College of Rheumatology 20% improvement criteria (ACR20) for PsA and the Psoriasis Area Severity Index 75% improvement score (PASI75) for psoriasis. Additionally, we will determine the number of serious adverse events and withdrawals due to adverse events.

Perspectives: This systematic review and meta-analysis will help facilitate evidence-based management, identify key areas for future research, and help provide a framework for conducting systematic reviews combining direct and indirect comparisons in both PsA and psoriasis.

INTRODUCTION

Rationale

Psoriatic arthritis (PsA) is a chronic inflammatory disorder, which is associated with skin psoriasis (1). PsA affects approximately 30% of patients with psoriasis and the typical onset of PsA occurs during the fourth decade of life (2, 3). The clinical presentation of PsA is heterogeneous; primary characteristics are peripheral joint inflammation, nail involvement, axial skeleton disorders, enthesitis, tenosynovitis and dactylitis (4). Approximately 40 – 60% of patients with PsA develop erosive and deforming joint complications and the disease may lead to progressive disability and pain (4, 5). Psoriasis is as well a chronic, relapsing and remitting inflammatory disease with a prevalence of approximately 3% worldwide (6). PsA and psoriasis are closely related diseases; nearly all patients with PsA also have active psoriasis and a considerable amount of the patients with psoriasis have joint symptoms, although these may not always be diagnosed (7, 8). Also, from a pathophysiological perspective, the diseases share significant similarities (8). PsA and psoriasis are associated with several severe comorbidities and risk factors, including cardiovascular disease, metabolic syndrome, obesity, diabetes, liver disease, depression, anxiety, and reduced quality of life (1, 9, 10). The term "psoriatic disease" is a generally accepted term, which covers all different aspects of these diverse clinical characteristics (9).

Over the last decades, the management of PsA and psoriasis has markedly improved, especially due to the introduction of biological disease modifying anti-rheumatic drugs (bDMARDs) such as the tumour necrosis factor inhibitors (TNFi) (11-13). In both PsA and psoriasis, bDMARDs have shown clinically relevant response rates (9, 14). However, due to the complexity and clinical heterogeneity of the diseases, adequate treatment is still challenging, e.g. 40% of patients with PsA do not achieve a clinically significant improvement within 1 year (15, 16) These limitations in combination with the high costs associated with bDMARDs have led to a continued search for new targeted therapies (bDMARDs and oral targeted synthetic DMARDs [tsDMARDs]) for both PsA and psoriasis (17). In recent years, the bDMARDs ixekizumab (IL-17a inhibitor), secukinumab (IL-17 inhibitor) and ustekinumab (interleukin [IL]-12/IL-23 inhibitor), and the tsDMARD apremilast (phosphodiesterase-4 inhibitor), have been approved by the European Medicines Agency (EMA) and The US Food and Drug Administration (FDA) for the treatment of PsA and/or psoriasis. The advent of these targeted therapies (i.e. bDMARDs and tsDMARDs) has increased the number of therapeutic options for patients with PsA and psoriasis (9, 15, 17). Ideally, a single therapeutic agent would control both the joint and skin psoriatic symptoms (7). With several new types of treatments available and lack of information on differential efficacy and safety,

therapeutic decisions in clinical practice remain challenging (11).

Meta-analyses of randomised controlled trials (RCTs) are one of the most reliable sources of evidence for evaluation of intervention effects (18). However, the value of inference from a meta-analysis depend on the internal validity and homogeneity of the included trials (19). Studies in other rheumatic diseases testing targeted therapies indicate that the trials often vary with respect to certain factors including eligibility criteria and baseline characteristics (20). Trial characteristics in RCTs generally cover a broad range of variables such as evaluated intervention and comparators, allowed concomitant medication, specific patient inclusion and exclusion criteria (e.g. type of disease; allowed comorbidity; level of disease activity; disease duration; gender; age; race), and trial design (e.g. blinding of participants, personal and outcome assessors; early rescue opportunities; trial duration). The patient baseline characteristics in a given trial will therefore be a product of the trial characteristics. When evaluating various interventions with a given outcome it is important to consider the context in which the trial is performed. What works in one context may not work in another (21, 22).

Contextual factors are well known from the framework of the International Classification of Functioning, Disability, and Health (ICF), which provides a complex health model in which variables beyond the disease can act as facilitators or barriers for an outcome (23). Contextual factors in the ICF framework are personal factors such as race, sex, age, educational level etc., and environmental factors, which are not directly within the person's control such as laws, cultural believes, family and work. However, no agreement exists with regard to the contextual factors that are relevant in clinical studies (24). Contextual factors can be defined as factors that are not the primary focus of the trial, but that may influence on the results and they could be classified as potential confounders, mediators, effect modifiers, or even independent predictors (24). As the treatment possibilities for PsA and psoriasis improve there is an increasing need to explore which patients are more likely to respond well to one intervention compared with another (25, 26).

It is not known to which extent the choice of inclusion and exclusion criteria and the following characteristics of included patients modify the treatment response in trials of targeted therapies in PsA and psoriasis. Knowledge about whether certain variables and contextual factors modify treatment effect may be important for prognostic and health economic reasons and could influence on trial designs, clinicians, policy makers and the pharmaceutical industry.

Objectives

The main objective of the current study is to assess the importance of trial and patient baseline characteristics when evaluating treatment response of targeted therapies for patients with PsA and psoriasis with the purpose of identifying prognostic factors of importance for treatment response (i.e. an effect modifier).

We aim to analyse the treatment effect of the targeted therapies in the two diseases, PsA and psoriasis, in combination, including RCTs on both PsA and psoriasis. However, we will also perform analyses in which we examine the treatment effect of the targeted therapies for each disease, one at a time. Additionally, we will determine how specific targeted therapies compare in terms of harm in adults with PsA and psoriasis with respect to the number of serious adverse events and withdrawals due to adverse events.

We hypothesise that the treatment effect of a therapy will depend on the disease (PsA/psoriasis) treated and that there will be a difference in treatment effect for different agents. Furthermore, we hypothesise that some trial characteristics can be considered important contextual factors as they are effect modifiers.

METHODS

Protocol and registration

Inclusion criteria and analyses methods for this systematic review and meta-analysis will be specified in advance and documented in this study protocol (27). The study protocol will be made publicly available at the international prospective register of systematic reviews - PROSPERO (http://www.crd.york.ac.uk/PROSPERO/). Registration number: CRD42016050049. The study findings will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) (28).

Eligibility criteria

Trial criteria: In the present systematic review we will include RCTs written in any language. However, only trials reported in English will be included in the meta-analysis. No restrictions in publication year will be applied.

Patient criteria: Patients should be adults (≥ 18 years) and have a diagnosis of PsA and/or psoriasis. We will exclude studies, which are entirely based on a subpopulation of the PsA/psoriasis patients (e.g. studies only assessing therapy effect on scalp psoriasis).

Intervention criteria: The interventions of interest will be targeted therapies with a standard route of administration and dosages approved by the EMA or the FDA for treating PsA or psoriasis. Biosimilar agents will be grouped with the reference product (29). Trials will be included if the targeted therapies are compared with any control (i.e. an active therapy or placebo). Concomitant allowed drug therapy (e.g. conventional synthetic disease modifying antirheumatic drugs [csDMARDs], retinoids, and topical agents) will be eligible if they are similar in all trial arms. We will exclude trials: (1) evaluating a combination of targeted therapies; (2) evaluating a targeted therapy in combination with a conventional therapy vs. the same targeted therapy as monotherapy; (3) evaluating same targeted therapy in combination with different types of conventional therapy (including different doses or administration form); (4) comparing targeted therapy continuation vs. targeted therapy discontinuation (i.e. withdrawal trial design); (5) evaluating different doses or administration frequencies of the same targeted therapy. Targeted therapies of interest for PsA will be adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab (Table 1a). Targeted therapies of interest for psoriasis will be adalimumab, apremilast, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab (Table 1b).

Outcome criteria: "Retention" will be considered as a measure of experienced treatment effect and be the primary outcome. Trials must report *Retention* at month 3 – 6 to be eligible for inclusion in the analysis (30).

Table 1a. Dosages of the bDMARDs and tsDMARDs for PsA, which will be included in the study.

Therapy of interest	Loading regime	Maintenance regime	Approval	
			EMA	FDA
Adalimumab*	None.	40 mg s.c. every 2 weeks.	X	X
Apremilast*	Tablets for oral use. Day 1: 10 mg in the morning. Day 2: 10 mg in the morning and 10 mg in the evening. Day 3: 10 mg in the morning and 20 mg in the evening. Day 4: 20 mg in the morning and 20 mg in the evening. Day 5: 20 mg in the morning and 30 mg in the evening. Day 6 and thereafter: 30 mg in the morning and 30 mg in the evening.	30 mg twice daily taken orally.	X	X
Certolizumab*	400 mg s.c. at week 0, 2 and 4.	200 mg s.c. every 2 weeks or 400 mg s.c. every 4 weeks.	X	X
Etanercept*	None.	50 mg s.c. once weekly or 25 mg s.c. twice weekly (the latter regime only approved by EMA).	X	X
Golimumab*	None.	50 mg s.c. once a month.	X	X
Infliximab*	5 mg/kg IV at week 0, 2 and 6.	5 mg/kg IV every 8 weeks.	X	X
Secukinumab D_1*	150 mg s.c. at week 0, 1, 2, 3, and 4.	150 mg s.c. every 4 weeks.	X	X
Secukinumab D_2§	300 mg s.c. at week 0, 1, 2, 3, and 4.	300 mg s.c. every 4 weeks.	X	X
Secukinumab D_3	None.	150 mg s.c. every 4 weeks.		X
Ustekinumab*	45 mg s.c. at week 0 and 4.	45 mg s.c. every 12 weeks.	X	X

* Primary dose. The primary dose will be included in the analyses. s.c.: subcutaneously; D: Dose. § Psoriatic arthritis patients with moderate to severe psoriasis.

Table 1b. Dosages of the bDMARDs and tsDMARDs for psoriasis, which will be included in the study.

Therapy of interest	Loading regime	Maintenance regime	Approval	
			EMA	FDA
Adalimumab*	80 mg s.c. at week 0.	40 mg s.c. every 2 weeks from week 1.	X	X
Apremilast*	Tablets for oral use. Day 1: 10 mg in the morning. Day 2: 10 mg in the morning and 10 mg in the evening. Day 3: 10 mg in the morning and 20 mg in the evening. Day 4: 20 mg in the morning and 20 mg in the evening. Day 5: 20 mg in the morning and 30 mg in the evening. Day 6 and thereafter: 30 mg in the morning and 30 mg in the evening.	30 mg twice daily taken orally, morning and evening.	X	X
Etanercept D_1*	50 mg s.c. twice weekly for 3 months.	50 mg s.c. once weekly or 25 mg s.c. twice weekly (the latter regime only approved by EMA).	X	X
Etanercept D_2	None.	50 mg s.c. once weekly or 25 mg s.c. twice weekly.	X	
Infliximab*	5 mg/kg IV at week 0, 2 and 6.	5 mg/kg IV every 8 weeks.	X	X
Ixekizumab*	160 mg s.c. at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12.	80 mg every 4 weeks.	X	X
Secukinumab*	300 mg s.c. at week 0, 1, 2, 3, and 4.	300 mg every 4 weeks.	X	X
Ustekinumab*	45 mg s.c. at week 0 and 4.	45 mg s.c. every 12 weeks.	X	X

* Primary dose. The primary dose will be included in the main analysis. s.c.: subcutaneously; D: Dose.

Information sources

We will identify studies by searching electronic databases and scanning reference lists of retained articles. The following databases will be used for the search: Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and MEDLINE (via PubMed). Additional reports identified in relevant systematic reviews not retrieved through the electronic databases will be collated. Relevant reports on EMA's and FDA's websites, and relevant pharmaceutical companies' website will be

scrutinised to identify unpublished trial data. ST developed the search strategy and ST and CB will carry out the search.

Search strategy

The search strategy will be published online.

PUBMED

("Randomized Controlled Trial"[ptyp] OR "Controlled Clinical Trial"[ptyp] OR "Multicenter Study"[ptyp] OR "random*"[tiab] OR "placebo"[tiab] OR "trial"[tiab] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh]) AND ("Arthritis, Psoriatic"[Mesh] OR "Psoriasis"[Mesh] OR Psoria*[TIAB]) AND ("Phosphodiesterase 4 Inhibitors"[Mesh] OR "Antibodies, Monoclonal"[Mesh] OR "Monokines"[Mesh] OR "Receptors, Tumor Necrosis Factor"[nm] OR TNFR : Fc OR "TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields] OR "enbrel"[All Fields] OR "infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "Remsima"[All Fields] OR "Inflectra"[All Fields] OR "remicade"[All Fields] OR "CT-P13"[All Fields] OR "mab ca2"[All Fields] OR "monoclonal antibody ca2"[All Fields] OR "adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields] OR "humira"[All Fields] OR "golimumab"[All Fields] OR "golimumab"[Supplementary Concept] OR "simponi"[All Fields] OR "cnto-148"[All Fields] OR "certolizumab"[All Fields] OR "certolizumab pegol"[Supplementary Concept] OR "CDP870"[All Fields] OR "cimzia"[All Fields] OR "Ustekinumab"[All Fields] OR "ustekinumab"[Supplementary Concept] OR "CNTO-1275"[All Fields] OR "Stelara"[All Fields] OR "Interleukin-23"[Mesh] OR "Interleukin-12"[Mesh] OR "Secukinumab"[All Fields] OR "AIN457"[All Fields] OR "secukinumab"[Supplementary Concept] OR "Interleukin-17"[Mesh] OR "Cosentyx"[All Fields] OR "apremilast"[Supplementary Concept] OR "Otezla"[All Fields] OR "CC-10004"[All Fields] OR "apremilast"[All Fields]) OR “LY2439821” [Supplementary Concept] OR “ixekizumab” [All Fields] OR “Taltz” [All Fields])

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 3

#14 Humira

#15 D2E7

#16 idec c2b8

#17 golimumab

#18 simponi

#19 cnto-148

#20 certolizumab

#21 CDP870

#22 cimzia

#23 "TNFR:Fc":ti,ab,kw (Word variations have been searched)

#24 MeSH descriptor: [Phosphodiesterase 4 Inhibitors] explode all trees

#25 Ustekinumab

#26 CNTO-1275

#27 Stelara

#28 MeSH descriptor: [Interleukin-23] explode all trees

#29 MeSH descriptor: [Interleukin-12] explode all trees

#30 MeSH descriptor: [Interleukin-17] explode all trees

#31 Secukinumab

#32 AIN457

#33 Cosentyx

#34 apremilast

#35 Otezla

#36 CC-10004

#37 CT-P13
#38 SB4
#39 HD203
#40 ixekizumab
#41 Taltz
#42 LY2439821
#43 #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
#44 MeSH descriptor: [Psoriasis] explode all trees
#45 MeSH descriptor: [Arthritis, Psoriatic] explode all trees
#46 Psoria*
#47 #44 or #45 or #46
#48 #43 and #47
#49 #48 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 apremilast OR CC-10004 OR Secukinumab OR AIN457 OR CNTO-1275 OR Ustekinumab OR ixekizumab OR LY2439821).

Trial records:

Data Management

Data will be extracted from the RCTs and registered in a pre-specified data form (Microsoft Excel 2010). To avoid double counting of studies that are published more than once, we will juxtapose author names, treatment comparisons, sample sizes, and outcomes.

Selection Process

The procedure will consist of two phases: (1) Titles and abstracts of the references will be reviewed for relevant articles by one reviewer; and (2) two reviewers will independently evaluate the full text articles and the studies will be retained or excluded according to the pre-defined criteria.
Disagreements will be resolved by discussion and/or a consensus meeting with the other co-authors.

The PRISMA flow diagram will be used to summarise trial selection process and a complete reference list of all excluded references undergoing full text review will be reported.

Data collection process

A data extraction sheet will be developed a priori. Reviewers will extract data from the included trials, which subsequently will be verified by a second reviewer (CB, TSJ, MS). Disagreements will be solved by consensus e.g. by consulting a third author (ST, RC). If there is only one active arm it will be compared to the control arm. If there are two or more active arms evaluating an approved targeted therapy, the control arm will be divided by the number of active arms. Authors of included studies will be contacted by email, if the information required is not or is unclearly reported. A track record of contact will be collected and subsequently reported.

Data items

Trial background information: First author, trial publication year, superiority trial (yes, no), conventional therapy add-on-design (yes, no), open-label design (yes, no), continent(s), number of participants in the active trial arm(s), number of participants in the control trial arm(s).

Classification of eligibility criteria: Data will be obtained from the studies 'patients and methods' section or online available trial protocol (e.g. clinicaltrials.gov) and describe requirements for participants to enter the RCT as well as important matters regarding design. We will capture information on diagnosis (PsA/psoriasis), minimum required disease duration (years), maximum required disease duration (years), minimum required swollen joint count (number out of total evaluated), minimum required tender joint count (number out of total evaluated), minimum required stable plaque psoriasis (cm), required active skin psoriasis or a documented history of psoriasis (yes, no), minimum required body surface area (BSA) (0-100%), minimum required Psoriasis Area Severity Index (PASI) score (0-72), required meeting the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria (yes, no), comorbidity study (yes, no), required negative rheumatoid factor (yes, no), minimum required Dermatology Quality of Life Index (DLQI) (0-30), and minimum required Physician's Global Assessment (PGA) (severity), required one of the following: C-reactive protein (CRP) $\geq$ 15 mg/litre, erythrocyte sedimentation rate (ESR) $\geq$ 28 mm/hour and/or morning stiffness.

Regarding the medication history of the eligible population, we will categorise into groups. Conventional therapy will here be defined as csDMARDs (e.g. methotrexate) for PsA and phototherapy/systemic therapy (calcipotriol, glucocorticoids, hydroxycarbamide, all retinoids including acitretin, fumarates, methotrexate, immunosuppresives [e.g. ciclosporin, tacrolimus, pimecrolimus]) for psoriasis. We will categorise into the following groups:

I.) Conventional therapy (except NSAID and local glucocorticoids): 1) not exhausted [conventional treatment naïve; have not exhausted the treatment potential of at least one type of conventional therapy]; 2) exhausted [i.e. candidate for targeted therapy according to current guidelines (11, 31); the disease has been inadequately controlled by conventional therapy; the patients have exhausted the treatment potential of at least one conventional therapy]; 3) mix of 1 and 2; 4) not reported.

II.) Conventional therapy at randomisation (except NSAID and local glucocorticoids): 1) naïve, 2) not using, 3) continued, 4) discontinued, 5) not reported.

III.) bDMARD history: 1) naïve; 2) experience allowed (incl. failure); 3) mix of 1 and 2; 4) not reported.

Classification of intervention: Name of therapy, route of administration, dose per administration (maintenance dosage), frequency of administrations per year, duration of therapy.

Medication:

We will stratify into one of the following therapy types:

I.) adalimumab
II.) apremilast
III.) certolizumab pegol
IV.) etanercept
V.) golimumab
VI.) infliximab
VII.) ixekizumab
VIII.) secukinumab
IX.) ustekinumab

We will also stratify into the following therapy groups:

I.) TNFi bDMARDs
- adalimumab
- certolizumab pegol
- etanercept

- golimumab
- infliximab

II.) Non-TNFi bDMARDs
- ixekizumab
- secukinumab
- ustekinumab

III.) tsDMARDs
- apremilast

Baseline characteristics: Patient characteristics at baseline will be extracted (aggregated values). If both median and mean values are given for continuous data we will extract the median: Female sex (%), race (white) (%), age (years), body mass index (BMI) (kg/m^2) or weight (kg), disease duration (years), patient's global assessment of disease activity (0-100), patient's assessment of pain (0-100), physician's global assessment of disease activity (0-100), swollen joint count (number and total evaluated), tender joint count (number and total evaluated), Disease Activity Score in 28 joints (DAS28) (0-10), dactylitis (number of patients), enthesitis (number of patients), BSA (0-100%), PASI score (0-72), the Health Assessment Questionnaire (HAQ) (0-3), 36-item short form health survey (SF-36) physical component summary score (0-100), SF-36 mental component summary score (0-100), DLQI (0-30), Psoriatic Arthritis Impact of Disease (PsAID) (0-10), and Physician's Global Assessment (PGA) (severity), CRP (mg/litre), and ESR (mm/hour), patients with PsA or a history of PsA (number), previous therapies: Topical, phototherapy, csDMARDs, targeted therapies (number of patients).

Outcome Assessment: Retention (i.e. completers), American College of Rheumatology 20% improvement criteria (ACR20), and PASI 75% improvement score (PASI75). We will also extract information on the number of patients, who withdrew therapy due to adverse events and the number of patients with at least one serious adverse event (Table 2).

Table 2. Extracted variables

Trial background information
First author
Trial publication year
Superiority design
Add-on design
Open-label design
Continent(s)
Number of patients in active trial arm(s)
Number of patients in comparator trial arm(s)
Classification of inclusion criteria
Diagnosis (psoriatic arthritis/psoriasis)
Minimum required disease duration
Maximum required disease duration
Minimum required swollen joint count
Minimum required tender joint count
Number of joints assessed
Minimum required stable plaque psoriasis
Required active skin psoriasis or a documented history of psoriasis
Minimum required BSA
Minimum required PASI
Required meeting CASPAR criteria
Comorbidity study
Required negative rheumatoid factor
Minimum required DLQI
Minimum required PGA
Required one of the following: CRP ≥ 15 mg/litre, ESR ≥ 28 mm/hour and/or morning stiffness
Medication history category
Alteration of treatment prior to trial randomisation
Participant characteristics
Female sex
Race
Median/mean age
Median/mean BMI
Median/mean weight
Median/mean disease duration
Median/mean patient’s global assessment of disease activity
Median/mean VAS pain
Median/mean physician's global assessment of disease activity
Median/mean swollen joint count
Median/mean tender joint count
Median/mean DAS28
Number of patients with dactylitis
Number of patients with enthesitis
Median/mean BSA
Median/mean PASI
Median/mean HAQ
Median/mean SF-36
Median/mean DLQI
Median/mean PsAID
Median/mean PGA
Median/mean CRP
Median/mean ESR

Number of patients with a history of PsA
Previous therapies (topical, phototherapy, csDMARDs, targeted therapies)

Classification of intervention
Name of therapy
Route of administration
Dose per administration
Frequency of administration per year
Duration of therapy

Outcome assessment
Psoriasis and psoriatic arthritis:
Retention
Number of patients who withdrew due to adverse events
Number of patients with serious adverse events
Psoriatic arthritis:
ACR20
Psoriasis:
PASI75

Abbreviations. BSA: Body surface area; PASI: Psoriasis Area Severity Index; CASPAR: Classification Criteria for Psoriatic Arthritis; DLQI: Dermatology Quality of Life Index; PGA: Physician's Global Assessment; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BMI: Body mass index; VAS: Visual Analogue Scale; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; SF-36: 36-item short form health survey; PsAID: Psoriatic Arthritis Impact of Disease; csDMARDs: Conventional synthetic disease modifying antirheumatic drugs; ACR20: American College of Rheumatology 20% improvement criteria; PASI75: PASI 75% improvement.

Outcomes and prioritisation

"Retention" will be considered a measure of experienced treatment effect and this will be the primary outcome across all trials (PsA and/or psoriasis). Anticipating that disease type (PsA or psoriasis) can be a significant factor, we will analyse retention separately in both conditions. Additionally, we have chosen outcomes of specific interest for both conditions; the ACR20 response as outcome for PsA and PASI75 as outcome for psoriasis. A known problem in PsA research is the lack of uniformly reported outcomes (32). However, we expect that ACR20 – although originally developed for rheumatoid arthritis - will be the most frequently reported outcome for PsA (33). PASI is the most widely used score in psoriasis trials (12). For harm outcome we will use the number of withdrawals due to adverse events, and the number of serious adverse events. Withdrawals due to adverse events are important because they reflect the ultimate decision of the participant and/or physician to discontinue treatment (34). Data synthesis will assess outcome data at 3 – 6 months (3 months will be prioritised), because achievement of target should be reached within 3 – 6 months. In the main analysis we will not look at trial extensions (week 50 - 52), because the interpretation of results become too complex and unclear due to crossover designs, rescue possibilities and therefore lack a relevant comparator group. Based on a previous similar

study in rheumatoid arthritis patients, we anticipate that it will be possible to identify predictors for the overall treatment effect within 3 – 6 months, which is the main aim of the current study (35).

Risk of bias in individual studies

The Cochrane Collaboration tool for assessing the risk of bias (RoB) for each trial will be used in this trial (36). The tool covers sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Two review authors will make the judgments independently. Disagreements will be resolved first by discussion and then by consulting a third author (RC) for arbitration. Each domain will be rated as "low", "high" or "unclear". Domains will be rated as unclear if they fail to meet the criteria for high or low RoB.

Data Synthesis

Data synthesis will assess outcome data at 3 – 6 months. *Retention* will be analysed for all patients with PsA and/or psoriasis comparing targeted therapy with a control arm (i.e. the overall model). We will, however, perform analyses in which we will stratify by disease (PsA or psoriasis). Furthermore, we will stratify by trial design (superiority design [yes, no], add-on design [yes, no], open-label [yes, no]) with the purpose of basing the primary analyses on non-open-label, superiority, add-on trial designs (i.e. exclusion of head-to-head trials of targeted therapies, head-to-head trials of targeted therapy and conventional therapy, inferiority trials, and open-label trials).

Treatment effect: For each trial, we will estimate the odds ratio (OR) and the corresponding standard error (SE[logOR]) based on the intra-trial contrast between active intervention and comparator group. Results will be reported with 95% confidence intervals (95% CI).

Heterogeneity: We will test for heterogeneity with the Cochran's Q-test and calculate the I^2 statistic to describe the percentage of total variation across trials, that is attributable to heterogeneity rather than to chance (I^2) (37, 38). If high levels of inconsistency among the trials exist ($I^2 \geq 50\%$) the trial design and characteristics in the included studies will be further explored. We will try to explain the source of heterogeneity in subsequent stratified analyses. We will compute homogeneity statistics to evaluate the consistency of the individual trial results when based on a fixed-effect meta-analytic summary; however, we use standard random-effects meta-analysis as default option, whereas the fixed-effect analysis will be applied for the purpose of sensitivity analysis.

Effect modification: We will explore potential effect modification of trial eligibility criteria and patient baseline characteristics, in a number of stratified meta-regression analyses. These analyses will be modelled using Restricted Maximum Likelihood (REML)-based models. A priori, we define a relevant trial-level covariate as one that decreases the between-trial variance (τ^2, estimated as Tau-squared [T^2]) as a consequence of inclusion in the (mixed effects) statistical model. Comparisons between different trial eligibility criteria or patient baseline characteristics will be presented as Ratio of Odds Ratios (ROR) with a 95% confidence interval (95% CI).

Analyses tools: Analyses will be performed using Review Manager for basic meta-analyses (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), and SAS software for the (multivariable) meta-regression models (version 9.3, by SAS Institute Inc., Cary, NC, USA).

Missing data:

We will contact the authors of the trial to obtain relevant missing data. Important numerical data will be carefully evaluated. If missing data cannot be obtained, an imputation method will be used.

Confidence in cumulative evidence:

The quality of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology (39). The quality of evidence will be assessed across the following domains: Risk of bias, consistency, directness, precision, and publication bias. Additional domains may be considered where appropriate. Quality of evidence will be evaluated as high, moderate, low or very low.

PATIENT PERSPECTIVES

Two patient experts have been consulted to review the protocol and confirmed the importance of the study from the perspective of patients. They will be involved throughout the research process, but in particular in the interpretation of the final results, contribute to the future research agenda and help with the dissemination of the outcomes. The project follows the EULAR recommendations (40) for the inclusion of patient research partners (41) (Table 3).

Table 3. PRP involvement according to EULAR recommendations.

1 Two PRPs have voluntarily participated in the process of designing and preparing the study protocol. They have read and commented on the protocol in its current form.
2 The PRPs endorsed the idea and purpose of the study and participated in discussions of relevance, ethics and design. PRPs and primary investigator will discuss the project process approximately every 6th month until the study is finalised.
3 The two PRPs have psoriasis and concomitant psoriatic arthritis.
4 The Danish PRP was identified during routine care. Prior to their decision of participation she received a written and oral task description that clarified her role and expected contributions.
5 The two PRPs expressed a serious and constructive interest in the research collaboration and showed good communication skills.
6 The primary investigator will continuously consider the specific needs of the PRPs, including educational aspects. A safe and respectful environment is highly prioritised and the PRPs may contact the research group whenever needed.
7 The investigators provide information and appropriate training, including awareness of ethical issues throughout the study.
8 The PRP work voluntarily and have been offered co-authorship according to the International Committee of Medical Journal Editors criteria.

Abbreviations. PRP: Patient research partner.

ETHICS

As no primary data collection will be undertaken, no additional formal ethical assessment and informed consent are required.

DISSEMINATION

The dissemination goal is to help clinicians make evidence-based decisions and give guideline developers an updated evidence synthesis based on the available research. Based on previous meta-analysis (42, 43), we anticipate that there will be few studies about the use of ustekinumab in PsA and for this agent we are aware that the power may be insufficient. However, we will include ustekinumab for PsA and psoriasis, because we wish to take all targeted therapies into account. This systematic review and meta-analysis will identify predictors for overall treatment effect, identify key areas for future research, and help provide a framework for conducting large systematic reviews combining direct and indirect comparisons in both PsA and psoriasis. The findings of the project will result in a scientific publication in an international peer-reviewed journal. The trial results will be presented at international professional meetings as well as to professionals and patients, who take an interest in the modern therapy of PsA and psoriasis.

FUNDING

The Parker Institute is supported by grants from the Oak Foundation; in order to cover the cost of having research fellows with clinical epidemiological skills employed, several mutually independent sources will be applied for.

TIMELINE

June – October 2016: Protocol.

November 2016: Search and trial selection.

December 2016: Data extraction.

January 2017: Statistical analyses.

January 31st, 2017: Abstract submission EULAR (Madrid 2017)

February 2017: Manuscript submission.

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